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Requirements of mouse models by Pharmaceutical Industry. EFPIA opinions

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Disclaimer

- Informations compiled in this presentation are the opinion of several experts from different EFPIA companies. Nevertheless, this presentation does not represent EFPIA's official position, as it has not been reviewed, discussed, and agreed with all members.

Use of the mouse as an animal model in preclinical/clinical development

- The use of transgenic mouse models is key for the validation of a new target
- The mouse is often used as the initial animal model for obtaining pharmacological data in a drug discovery programme, especially for small molecules
- According to Regulatory Guidelines, the mouse could be one of the two required animal species (the rodent one) for preclinical safety evaluation of drugs: assessment of general toxicity, safety pharmacology, development and reproductive toxicology, mutagenicity and carcinogenicity
- In some cases (especially for biologics), transgenic/humanized mouse models are the only animal models available for safety assessment

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Mouse models: advantages

- For small molecules, mouse is scientifically acceptable in most cases, provided that (i) the target is adequately expressed and (ii) the metabolism is not so different than that of humans
- As initial pharmacology/efficacy data is often obtained in mice, PK-PD relationships can be rapidly established. Safety margins can also be assessed very soon
- For biologics, mouse is often used as rodent species, because the use of knock-in mice is possible and surrogate monoclonal antibodies may be available
- Compound requirement for animal testing is ~10 fold less with mice compared to rats, an important issue in drug discovery logistics

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Mouse models: disadvantages

- Rat is often preferred as rodent species for toxicity evaluation, more for practical than scientific reasons:
  - More historical data available
  - Larger volumes of blood available for analyses (less true now with microsampling techniques)
  - Higher background noise for malformations in mice (drawback for teratogenicity studies). Rabbit is also used in these studies
- Robustness and predictivity of mouse models are variable. Many failures have occurred when metabolic profile, clearance, and target tissue expression are not representative of human situation (but the same applies to rat models!)

Industry requirements regarding mouse model development (efficacy and DMPK)

- There is an agreement that mouse models have value in Drug Discovery and Development so efforts to improve them are valuable
- Beyond the mere use of genetic models, there is a demand for ‘humanized mice’ in order to increase predictivity and therefore translatability to the human situation. These could also be useful for metabolism and PK studies to predict human kinetics and drug-drug interactions. Some experts demand mice with humanized liver or immune systems, as a very useful tool to understand differences among species

Industry requirements regarding mouse model development (safety)

- Less interest for safety evaluation in disease models. Until now, toxicology evaluation requires non pathology models
- Although recognizing the value of safety profiling in a disease model, this should be accepted by Regulatory Authorities. They might ask for a significant validation and only accept it on a case-by-case basis
- Knock-in/humanized mice models might be useful for safety evaluation when neither rats nor normal mice can be used (particularly in some biologics)

Other remarks

- A clinical researcher pointed out the importance of the translation of mouse models to the predictability of early clinical safety and demand more efforts on translational research
- An expert demands more interest in rat models, as rats are the standard rodent species for many studies and there is a lot of data available. New technologies are now available for general and tissue-specific KO rat development

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