Transgenic / Chimeric NHP Neuroscience Opportunities and Challenges

Contributions to the assessment from a European perspective

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NHP research in Europe

- Animal research in Europe:
  - ~ 12 Mill. animals/year (vertebrates, i.e. including rodents); ca. ¾ in UK, France, Germany
    - ~ 75% rodents (~50% transgenic),
    - ~ 15% cold-blooded animals (reptiles, amphibians, fish)
    - ~ 0.05 % (1 : 2,000) non-human primates[1]
  - Animal research in the broader context of societal use of animals:
    - Human meat consumption: ~ 500,000 animals for every NHP in research.

[1] Small proportion belies the scientific importance of NHP, but rather reflects the practical, resource and financial challenges of NHP research

NHP research in Europe

- Animal research purposes in Europe:
  - Toxicology (+ product development):
    - Across all species: < 10% (40%)
    - for NHP: > 50% (80%)
  - 'Fundamental' research
    - All species: 46%
    - For NHP: 10%
- Non-commercial NHP neuroscience research
  - Distributed across national primate centers and academic laboratories (within and outside universities)
  - This dual approach is essential for optimally serving the role of NHP research
  - The unique resources of primate centers will play a central role in developing and maintaining transgenic NHP lines

Legal Framework: The EU Directive

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DIRECTIVES

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

(Text with EEA relevance)

The EU Directive

- Passed 2010
- Transposed into national laws
- Core rules:
  - 3R-Approach as a central principle
  - Covers vertebrates & cephalopods
  - Special rules for NHP, incl. prohibition to use of great apes[1]
  - Definition of procedures: >= introduction of a needle; incl. creating genetically modified animal lines; excludes killing for organ/tissue use
  - 3 severity categories (mild, moderate, severe)
  - Institutional animal-welfare body
  - National/regional competent authority
  - Authorization decisions within 40 days

1: Last use of great apes in EU in 1999

Animal welfare

- All organisms are mutants, thus animals genetically modified on purpose should be treated just like animals where the genetic modification happened naturally
- Particular challenge of transgenic animals: disease models
  - require development of assessment techniques, both for scientific ‘success’ and potential suffering
  - staff training even more important than for NHP in general
- For new technologies specialized centers have a central role in developing and maintaining transgenic NHP lines as well in developing updated SOPs for animal husbandry and handling
- Reminder: 3R-principle and harm-benefit analysis are central to the concept of ethically justified animal research across **all** species
- For transgenic animals: special focus on harm inflicted by the genetic modification

‚Humanized' animal models

Special issue with genetically modifying NHPs:

Does a 'humanization' of non-human primates create individuals that make them more human-like in terms of the ethically relevant human vs. non-human differences ?

- Purpose of genetic modification
- Choice of species
- Xenotransplantation of neural tissue
- Brain organoids
- Main issue is not 'humanization', but the generation of individuals with unintended detrimental modifications

Communication

- Publicly funded research has the duty to communicate its use of tax resources
- This is especially important for ethically challenging types of research where society has developed a framework for dealing with the ethical dilemma
- Science is barely meeting this duty for regular animal research
- -> a need for a substantial push for pro-active communication on the when, why and how of animal research
- This is particularly important when new technologies are implemented as it needs to be communicated whether and how they affect the harm-benefit analysis and that this likely will increase the proportion and number of NHPs in research
- Pro-active communication should not be viewed as a nuisance, but as an opportunity

Conclusions

- Many of the issues of the enormous scientific and medical potential of introducing transgenic NHP into the tool chest of animal research can be addressed within the existing frameworks for all animal research
- Special issues are
  - Evaluating the scientific success of the manipulation
  - Assessing the severity of the animals' state, including 'collateral' modifications
  - Ensuring staff proficiency when dealing with disease models
  - Policy issue: centralization of transgenic facilities ?
  - Given the move from a research focus on healthy animals to focus on disease models there is an even greater need for pro-active communication with society[1]

[1] Including an understanding of the need of a large number of research projects with no *direct* medical benefit