TI PHARMA

Use of animals in pharmaceuticals

The future of non human primate use in the development of monoclonal antibodies

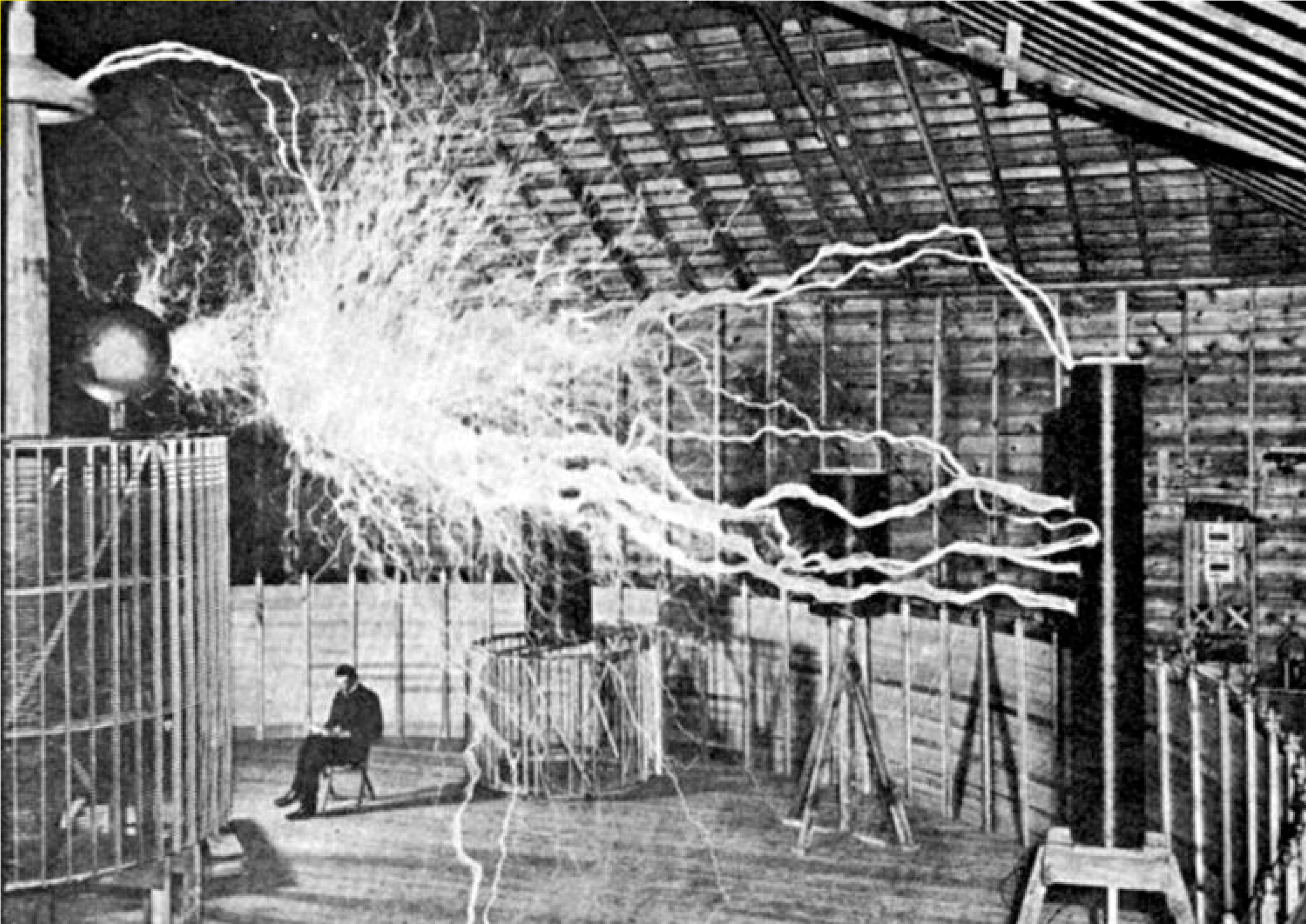
Universiteit Utrecht

This study/ work was performed (partly) within the framework of the Dutch Top Institute Pharma project T6-301.

Peter van Meer

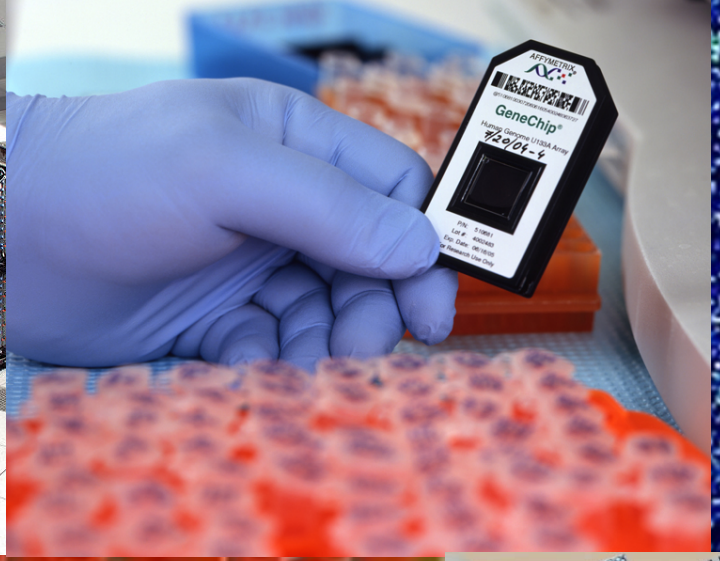
09-05-2012

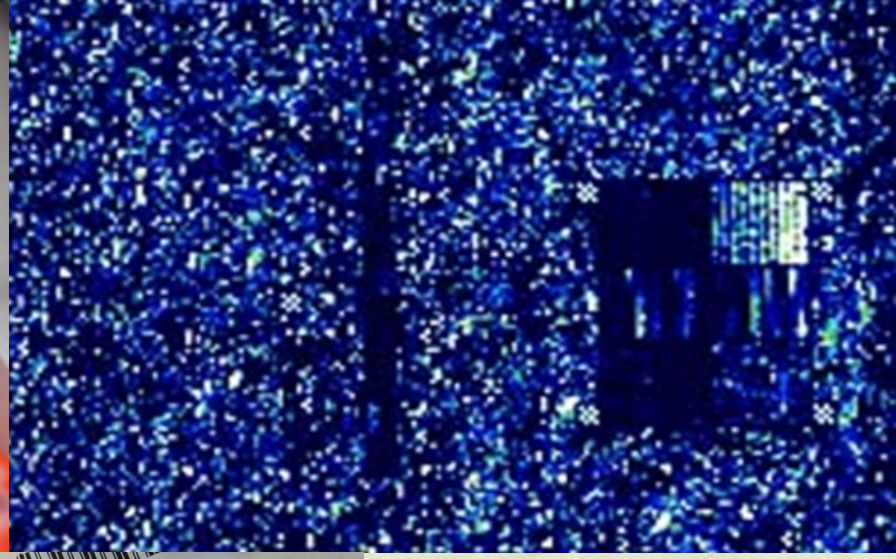
jointly shaping the future of medicine

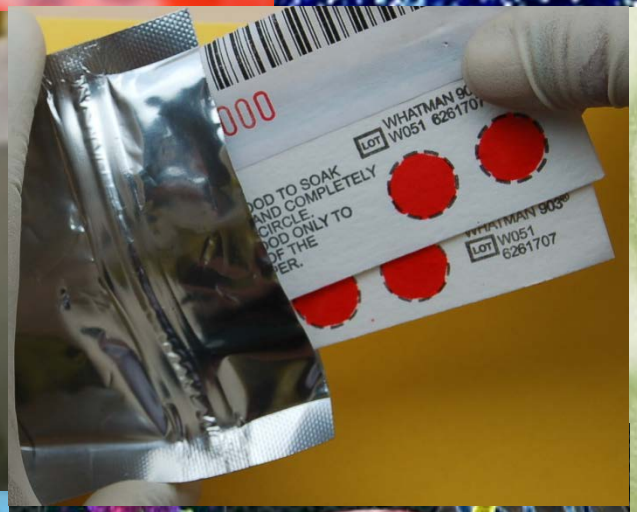


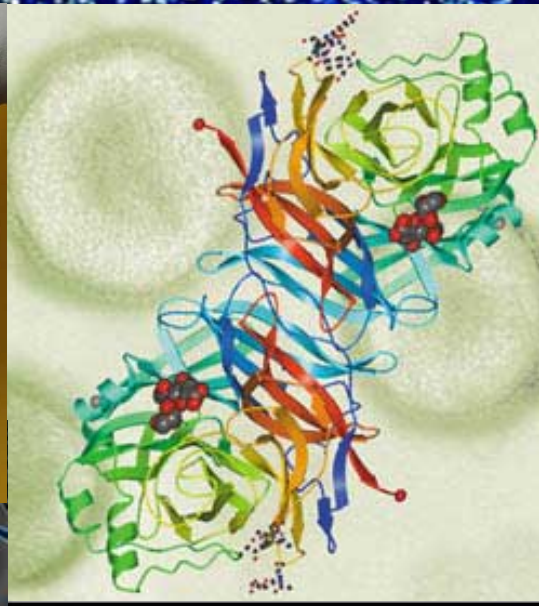
NBRP No. 0469
Wistar-Tg(GnRH-EGFP)Nphy
// 週齢
2008 7 2

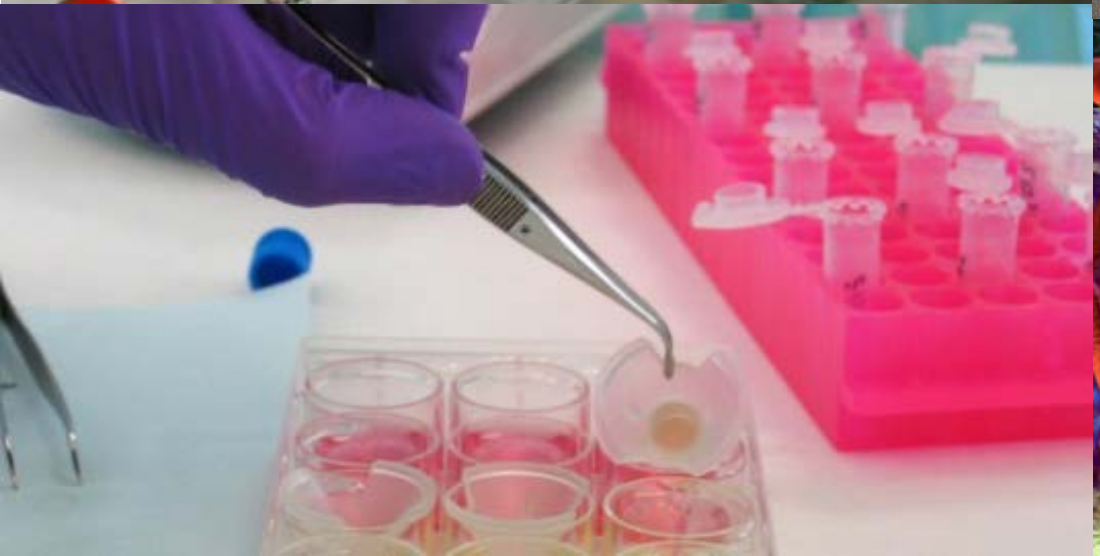
Blue Gene/P

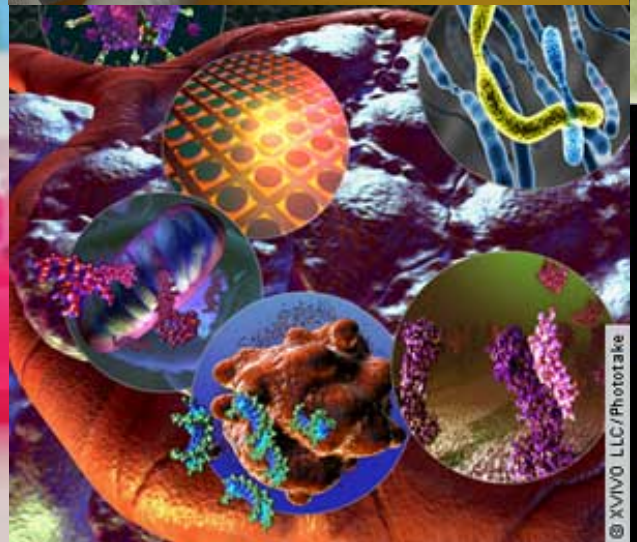

AFFYMETRIX
GeneChip

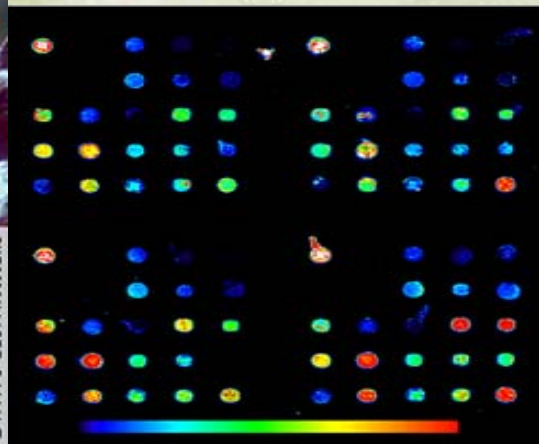



WHATMAN 90
LOT W051 6261707
LOT W051
6261707






© XVIVO LLC/Phototake



TI PHARMA
Use of animals in pharmaceuticals

Use of NHPs is ethically and scientifically problematic

Strong public opinion on ethics of using NHP

Predictive value?

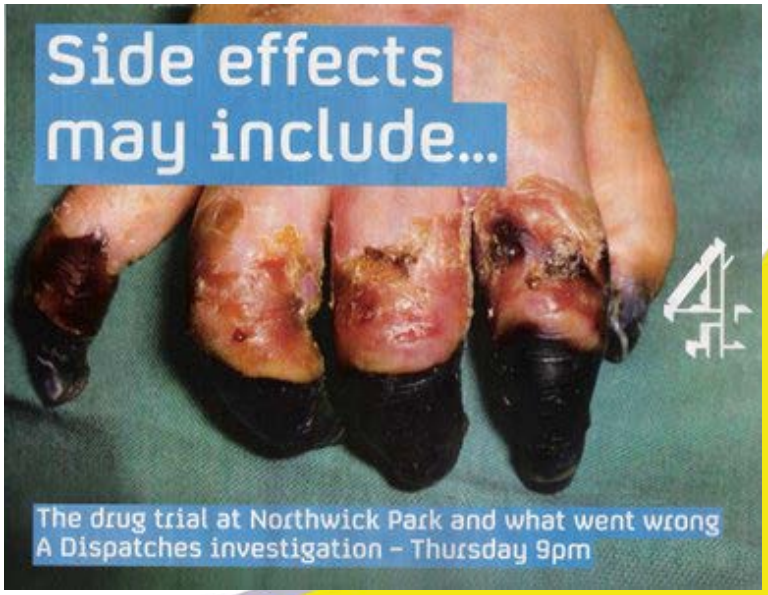
TGN1412, Herceptin

NHP use in drug development is increasing

CHIMPANZEE RESEARCH ON TRIAL

As pressure from activists builds, the United States is considering whether it should end invasive experiments in chimpanzees.

Wadman, Nature, Vol 474, Jun 2011



"We saw human guinea pigs explode" – *Sun*
"His head had swollen three times its normal size. None of us recognized him" – *Daily Star*
"It felt like a truck had been parked on my head. Then, somehow, the pain got worse" -*Sun*

TI PHARMA
Use of animals in pharmaceuticals

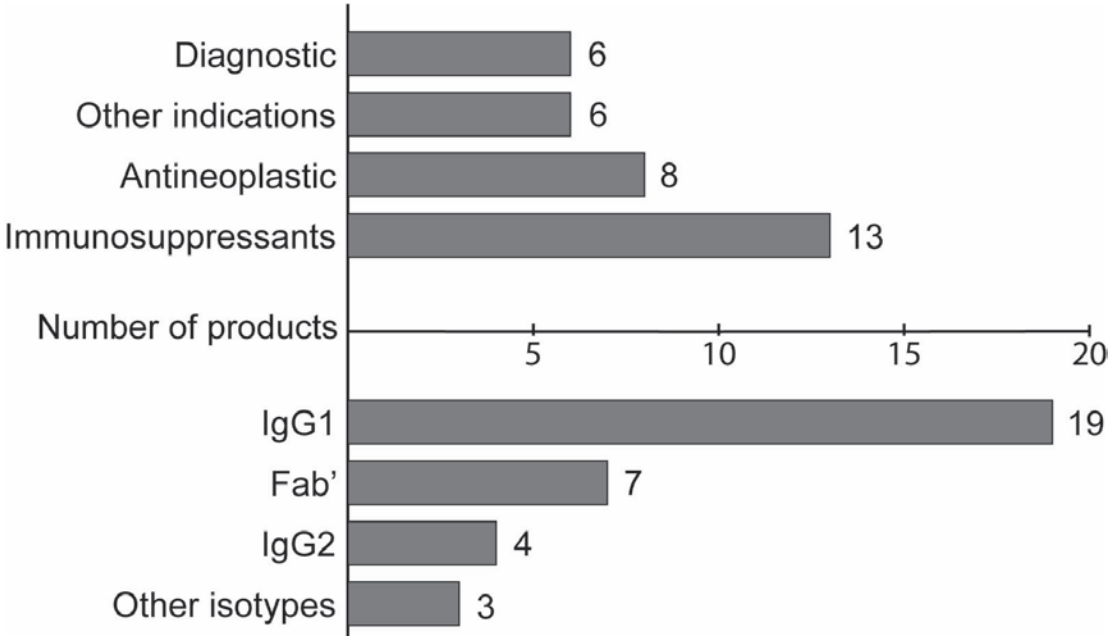
Study the relevance and value of the NHP model in regulatory animal studies

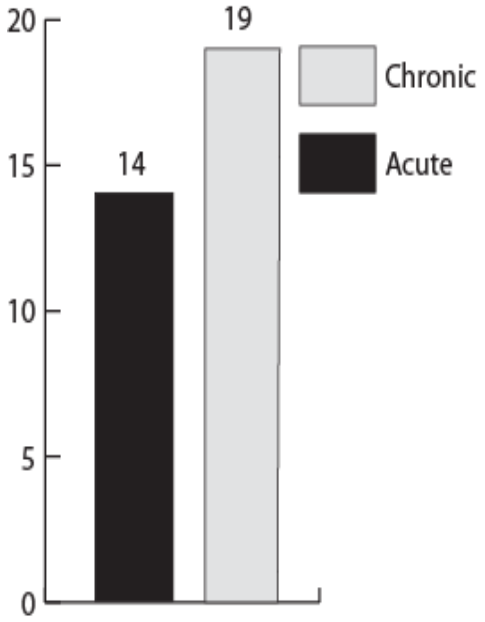
Almost 30 years of experience developing MAbs

What was the value of NHP in MAb development?

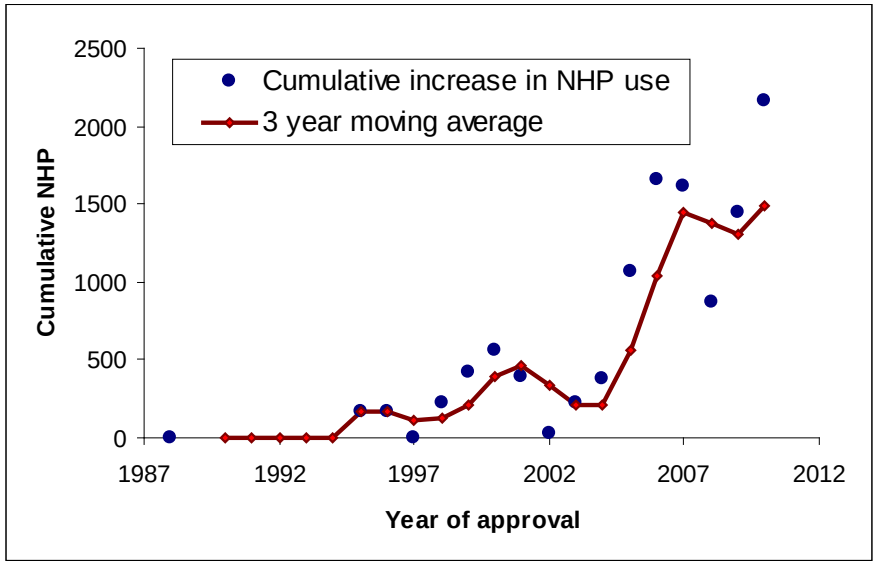
33 monoclonal antibodies have been registered in the EU by the EMA

Centralized approval between 1988-2010



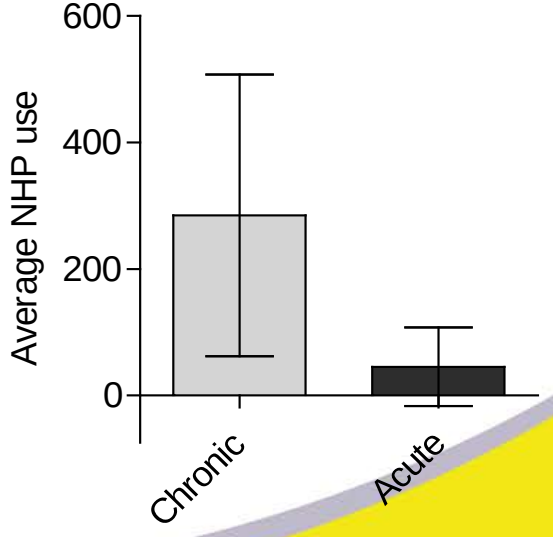


The number of nonhuman primates used for the development of monoclonal antibodies is increasing



Species	NHP (n)
Cynomolgus	5188 (24)
Marmoset	388 (2)
Rhesus	379 (6)
Chimpanzee	68 (3)
Baboon	18 (1)
African Green	9 (1)

	Chronic	Acute
Average NHP/product	285±223	45±62
Min/Max NHP/product	0/755	1/164
Average studies/product	12±6	6± 7
Min/Max studies/product	4/31	1/22



Known effects

Only pharmacological effects

Safety profile of MABs in NHP

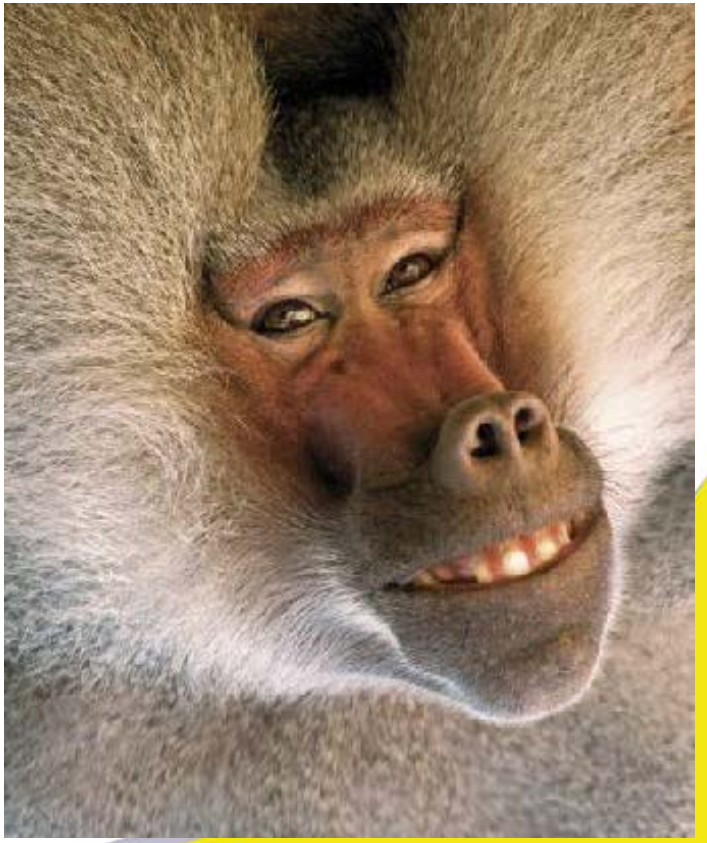
- 60% of MAbs were well tolerated or had minimal pharmacological adverse effects

- 40% (exaggerated) pharmacology or immune reactions, including DART

- The human side effect profile also limited to pharmacology and/or immunogenicity.

Use of necropsy

- Supporting clinical observations, lab tests
- Did not result in new findings



Study Design and Model

Examples that limit the value of NHP use

Studies using chimpanzees

- Poor study design, sub-optimal dosing and study conduct
- Safety assessment not optimal for the patient population:
- Repeat in mice + surrogate MAb

Inconclusive results

- Sample size (hazard identification)
- Lack of experience with cyclosporine-a
- Wild caught / old monkeys
- ‘NHP may not represent human situation’

Immunogenicity

Immunogenicity of monoclonal antibodies in NHP limit their value

MAbs were immunogenic in NHP in almost every study (98%)

Highly immunogenic in 30% (8 cases)

Increased clearance in 78% (21 cases)

Limited duration of chronic toxicity studies in 19% (5 cases)

Interpretation (PK and/or PD) limited in 44% (12 cases)

The value of NHP research in MAb development

30 years of MAb development with NHP; a **knowledge base**

The scientific value of future NHP studies is **limited**:

- **Expected** pharmacology or secondary effects.
- **ADA**'s limit the interpretation and relevance of NHP
- **Study design** further reduces the relevance of NHPs.

Looking ahead

Limit the use of NHP in drug development

Industry

- **Minimal**/confirmatory studies
- **In vitro/surrogate** endpoints
- Make data **public**

Regulatory authorities

- Increase **scientific advice**
- **Discourage** check-box
- **Reduce** regulatory demands

Governments

- **Incentivize**

Acknowledgements

- **Universiteit Utrecht**
  - Huub Schellekens
  - Ellen Moors
  - Marlous Kooijman
- **CBG-MEB**
  - Christine Gispen-de Wied
  - Jan Willem van der Laan
- **University of Lisbon**
  - Beatriz Silva-Lima

TI PHARMA

Use of animals in pharmaceuticals

Study Design and Animal Model

Known Effects

Immunogenicity