CBG MEB
MEDICINES EVALUATION BOARD

A decade of 3Rs research at the MEB:

Realising an optimal safety and efficacy assessment with a minimum of animal studies

dr. Peter van Meer 13-02-2020

GOOD MEDICINES USED BETTER

Conflict of interest statement(s)

The statements and opinions in this presentation are not necessarily those of the EMA or, its working parties or expert groups. Reproduction is not permitted without express approval

I oppose the conduct of animal studies without a scientific basis

I had to compress a lot of science into a few slides. For more, see the references and speak with the authors!

This research was not generated in a vacuum

Animal studies are a necessary evil (?)

- The best test system available (then)
- Prevent disasters like thalidomide
- Establish safety that can not otherwise be done in humans
- But… Animals are still a black box. Predictive value is challenged in science
- Type 1/2 error…

Food for Thought Look Back in Anger – What Clinical Studies Tell Us About Preclinical Work

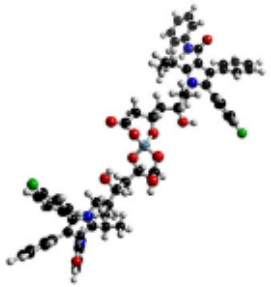
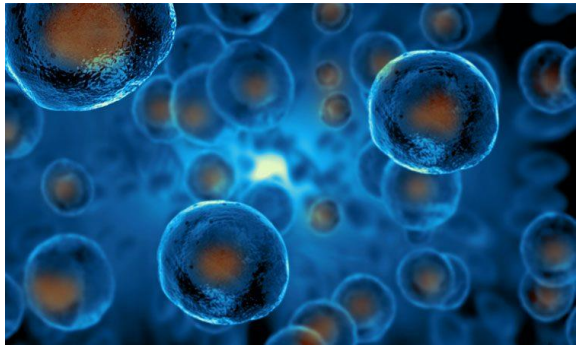
Thomas Hartung
Johns Hopkins University, Bloomberg School of Public Health, CAAt, Baltimore, USA and University of Konstanz, CAAT-Europe, Germany

Is poor research the cause of the declining productivity of the pharmaceutical industry? An industry in need of a paradigm shift

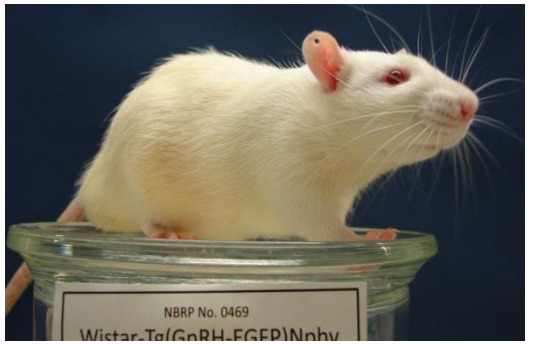
Frank Sams-Dodd[1,2]

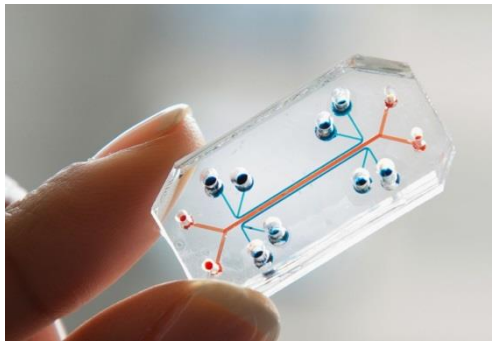
Crossing the threshold or stuck in a revolving door

- 20th century animal studies were intended for small molecules (20th century technology)
- 21st century technology to augment safety assessment and improved prognostic clinical relevance





Before 2010: who moves first

Safety studies in monoclonal antibodies (and biosimilars)

- Safety studies with mAbs primarily in NHP due to species specificity.
- ICH S6: Abbreviated study package.
- What has 30+ years of mAb development taught us?

- 60% of MAbs were well tolerated, 40% (exaggerated) pharmacology or immune reactions
- The human side effect profile also pharmacology and/or immunogenicity.
- Initial research suggests that long term studies do not reveal novel safety findings
- **The scientific value of multiple NHP studies is limited.**

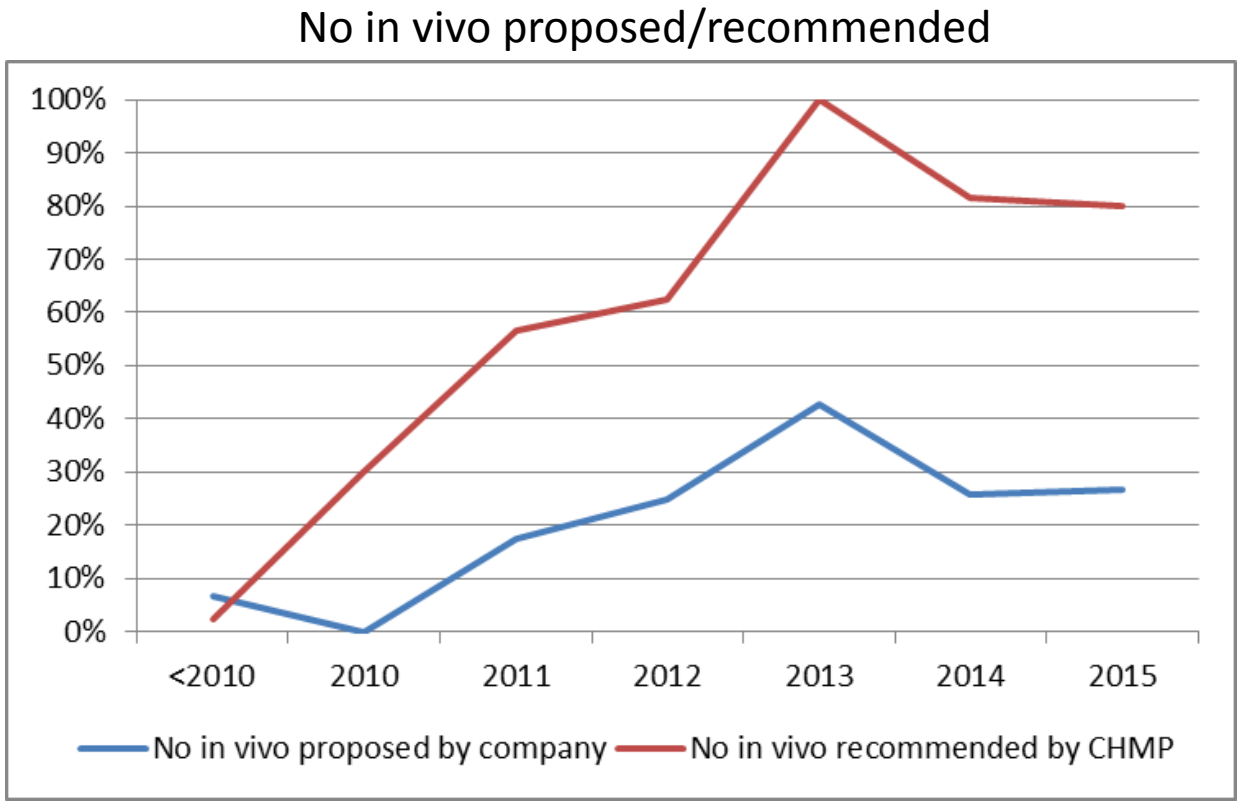
- Current research: optimal duration of safety studies (EPAA-NC3Rs), and need for multiple dose levels

van Meer et al. Nature Biotechnol. 2013 Oct;31(10):882-3

Safety studies in monoclonal antibodies (and biosimilars)

- Untill 2013 safety studies for copies of mAbs (biosimilars) were needed (comparative PD and toxicology).
- What was the value?

- Animal studies are not sensitive to demonstrate similarity (power, variability, reliability)
- Safety? Predictable or non-translatable
- EMEA/CHMP/BMWP/42832/2005 Rev. 1
- Quality is king
- **Risk based stepwise approach: no in vivo studies unless needed, in vitro**



van Aerts et al. Mabs 2014, 6:5, 1155-1162
van Meer et al. DDT 2015, 20(4):483-90

ICH S1: What do we do with carcinogenicity studies?

ICH S1 requires a 2-year rodent carcinogenicity study. Generally a tick box approach.

Can we predict a negative or positive outcome (and so do we need the study): New ICH process

- Positive prediction: Pre-existing evidence: pharmacology, positive classes, hormonal perturbation, immune suppression, induction of liver/thyroid effects
- Negative prediction: Based on absence of histopathology and negative pharmacological class.

Carcinogenicity Assessment	Human relevance
Class 1	Likely tumorigenic
Class 2	Uncertain (animal data might help)
Class 3A Class 3B	Not tumorigenic (3A) Irrelevant (Animal data don't help)

van der Laan et al. Crit Rev Toxicol. 2016 Aug;46(7):587-614
van der Laan et al. Front Med (Lausanne). 2016 Oct 14;3:45

ICH S1: What do we do with carcinogenicity studies?

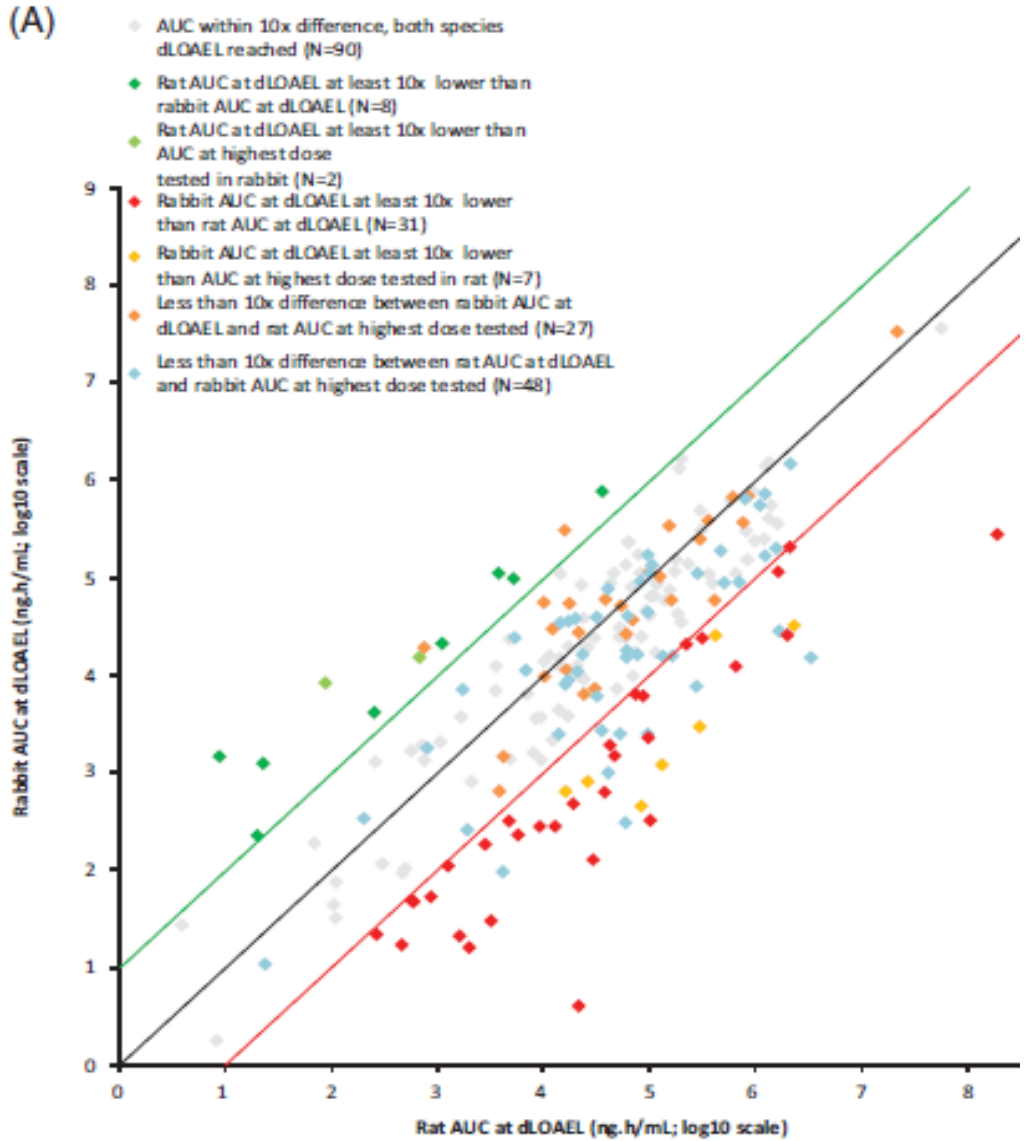
Total CAD count	**48**
Total Cat 3	32 (sponsor)
	24 (+1) (sponsor + DRAs)

- Category 3 evidence: Literature, chronic toxicology + genotoxicity data are clean or provide sufficient evidence, class data available
- Category 2 evidence: first in class, multiple drug targets, inconclusive literature/genotox, insufficient chronic toxicology data (metabolites, hormone effects, immunology data,…

- **Recommendations ICH S1**: Waiver based on preliminary evidence (CAD) is possible, discuss need for rat study early (end of Phase 2)
- *In vitro* Evidence generation for better in vitro predictivity: Poster of Britt Duijndam

ICH S5: Rat and rabbit developmental toxicity testing. Do we need both?

- Since thalidomide, 2 species reproductive toxicity testing is required (rat+rabbit).
- Are both species needed?
- **From phase 1 onwards, ICH S5** requires a EFD DRF, later embryofetal development in both species
- Analysis of ~380 pharmaceuticals with rat and rabbit data (including failed products)
- Rat and rabbit are relatively equal in sensitivity (NOAEL, LOAEL and HED).
- Also severity incidence is similar



Theunissen et al. Crit Rev Toxicol. 2016 Nov;46(10):900-910
Theunissen et al. Crit Rev Toxicol. 2017 May; 47(5):402-414

ICH S5: Rat and rabbit developmental toxicity testing. Do we need both?

- If they are comparable, you should be able to use just one species
- New ICH S5R3 revision proposes exactly that!
- **1 species DRF + (advanced) in vitro studies are sufficient before phase 3 + safety measures in phase 1/2**

deVolkskrant

Honderdduizenden minder proefdieren nodig

- Differences in NOAELs or LOAELs in developmental rat/rabbit toxicity studies… could just as well be caused by study replication errors, and not necessarily by differences in species sensitivity

Braakhuis et al. RTP 2019 Oct;107:104410

Advanced therapy medicinal products: too complex for animals?

TPI ATMP workshop 2019

"Coming up with good arguments to perform animal studies for ATMPs is difficult, not doing them is even more difficult"

- Rational hypothesis driven studies with human relevance more important than the model system (vivo/vitro). For safety AND efficacy
- Still very much a learning development: increased call for transparency/sharing
- Novel in vitro technologies are acceptable alternatives to conventional animal studies, but some remain necessary for now (e.g. biodistribution)
- The more we know…
  - If there is previous clinical experience, there is less/no need for studies. In vitro data can further contribute to the waiver of animal studies (eg tumorigenicity)
- **"No, unless" can be the basis of a new guideline**

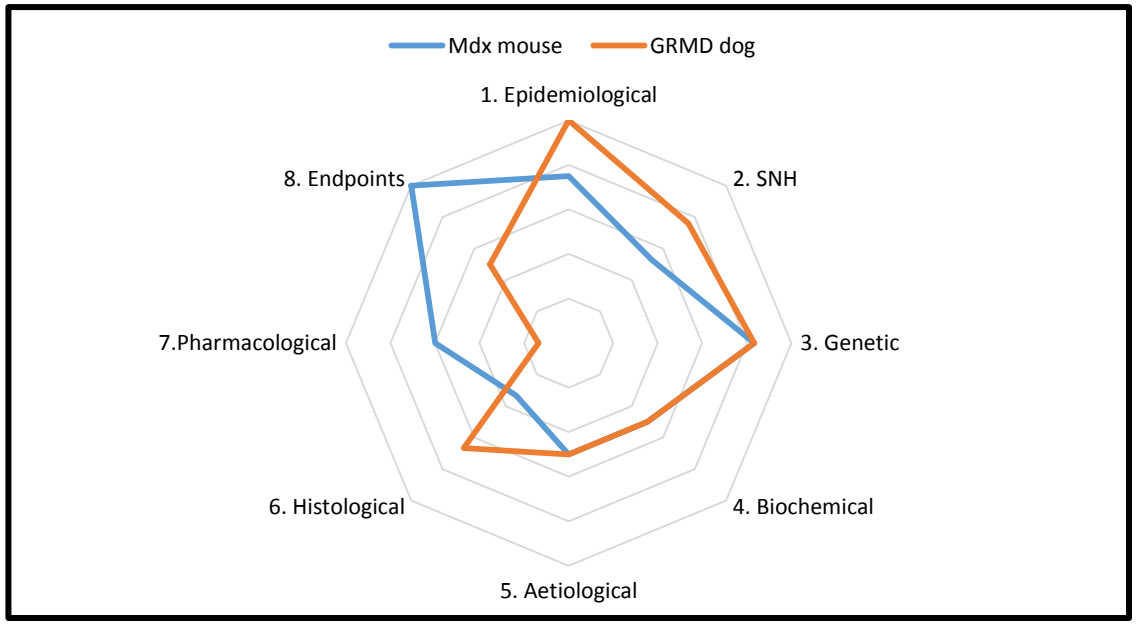
Off the beaten path: how relevant are animal models of disease?

- Reproducibility of animal studies (pharmacology) is low. This costs a lot of money. Not just in academia…
- Can we develop methods to discriminate between relevant and irrelevant animal models of disease?

- Standardised framework to identify and discriminate models of disease for drug efficacy (FIMD) based on 8 key characteristics

Ferreira et al. PLoS One. 2019 Jun 13;14(6)

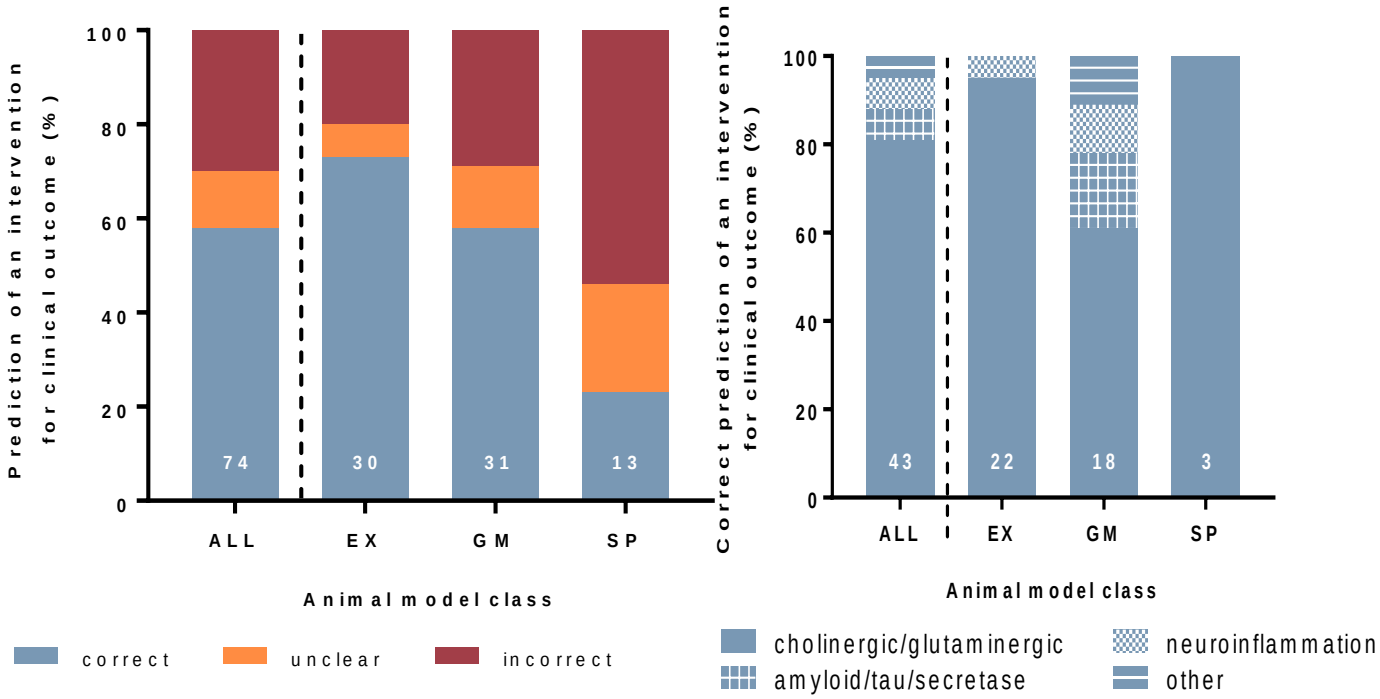
Publication	Percentage irreproducibility
Begly and Ellis (Amgen)	89% (n=53)
Prinz et al. (Bayer Healthcare)	78 (n=67)
Vasilevsky et al.	54 (n=238)
Hartshorne and Schachner	51 (n=257)
US annual preclinical research	**56.4 billion**



Off the beaten path: how relevant are animal models of disease?

Animal models of efficacy for Alzheimer's disease are poor predictors

- None of the 63 models were predictive
- insufficient understanding of the disease biology;
- testing a single hypothesis for a multifactorial disease;
- low internal validity of studies
- high variability in both choice and methodology of outcome measures.



- **External validity should be a key consideration to demonstrate value**

Veening et al. Eur J Pharmacol. 2019 Sep 15;859:172524

Final remarks: Time to look ahead

Research at the MEB has helped realise a tremendous reduction in the number of animals used in regulatory research… And has led to changes in international guidelines

There is still a lot to do!

- **No unless** should be the standard for future guidelines and revisions
- 21st century technology belongs in 21st century drug applications

So who moves first? **Who will come along?**

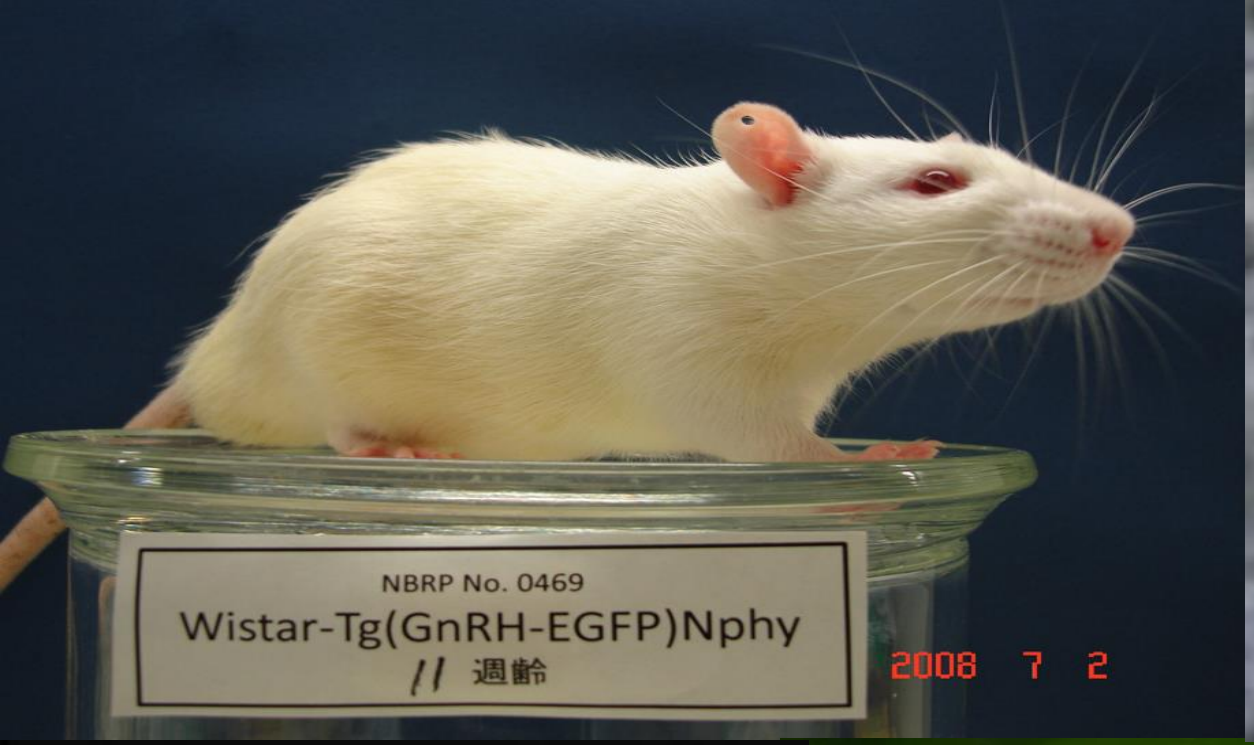
Acknowledgements

Many people contributed to this! In order of appearance:

Sylvia van Hulst (intern)
Leon van Aerts
Jan Willem van der Laan
Peter Theunissen
Tzu Chien (intern)
Tineke van den Hoorn
Charlotte de Wolf
Jorik Mulder (intern)
Tahira Nakdechi (intern)
Mariam Sadik (intern)

Guilherme Ferreira
Désirée Veening

National Institute for Public Health and Environment
Ministry of Agriculture, Nature and Food Quality
Ministry of Health, Welfare and Sport


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

CBG MEB

MEDICINES EVALUATION BOARD

GOOD MEDICINES USED BETTER