

# SYSTEMATIC REVIEWS & META-ANALYSES OF ANIMAL EXPERIMENTAL STUDIES – IMPROVING RESEARCH AND IMPLEMENTING THE 3 RS ?

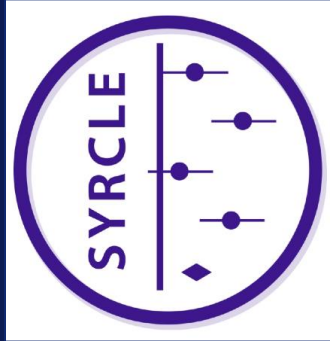
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Birgitte Kousholt, DVM, PhD,  
Department of Clinical Medicine  
Faculty of Health

# AUGUST – AARHUS UNIVERSITY GROUP FOR UNDERSTANDING SYSTEMATIC REVIEWS AND METAANALYSES IN TRANSLATIONAL PRECLINICAL SCIENCE

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AARHUS  
UNIVERSITET

# An upgrade of Animal Experimental Research Facilities • Research • Education



November 27th 2013 • 8.30 am – 3pm

AARHUS UNIVERSITY • HEALTH

AIAS • Høgh-Guldborgs Gade 6B • building 1632

DK-8000 Aarhus C

# DEPARTMENT OF CLINICAL MEDICINE

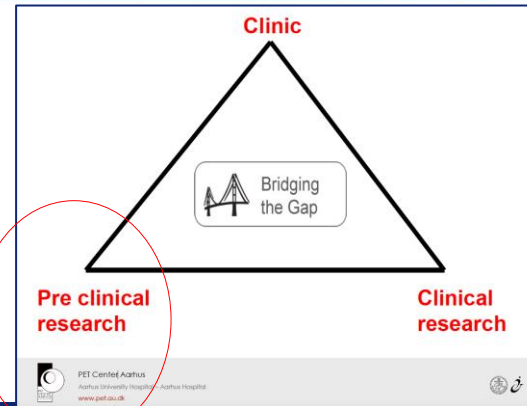
From basic research to clinical application

Formally established in 1972

140 full-time professors and associate professors

300 clinical and external associate professors

Approx. 2,100 publications annually



# PRECLINICAL ANIMAL STUDIES

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Translational research (and back-translation)

- Research from basic science is used as foundation for clinical research
- Research results from clinical science further investigated in animal models
- Develop a strategy to implement the 3 Rs at “baseline”

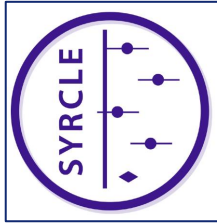
# THE LACK OF RIGOR..

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- ✧ ***” it seems natural to insist that animal research should be subject to the same rigorous methods used in clinical trials in human beings, yet such a point is sometimes viewed as controversial”***  
Sanderock & Roberts, 2002, the Lancet
  - ✧ ***“Where is the evidence that animal research benefits humans ? ”***  
Pound P et al 2004, BMJ
  - ✧ ***...ways to improve the yield from basic research should be investigated...***  
Chalmers et al in the Lancet 2014 “increasing value, reducing waste”

**=> WASTE – resulting from ignoring what is already known or already being researched....**



# ARE SYSTEMATIC REVIEWS THE BEST WAY TO IMPLEMENT THE 3 RS ?



No. of animal studies online

**Systematic review** a evidence-based literature search based on a single research question puts the same level of rigor to reviewing research evidence as should be used producing the research in the first place

**Meta-analysis** use of statistical methods to summarize the results of independent studies

# THE DIFFERENCE:

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## A Narrative Review:

- Subjective method
- General review question
- No specified study selection
- No attempts to avoid bias
- No combined data analysis
- The authors view substantiated by other researchers results

## A Systematic Review

- ✧ Evidence-based method
- ✧ Specific review question
- ✧ Transparent study selection
- ✧ Risk of bias analysis
- ✧ Meta-analysis of data



*Common in clinical practice*

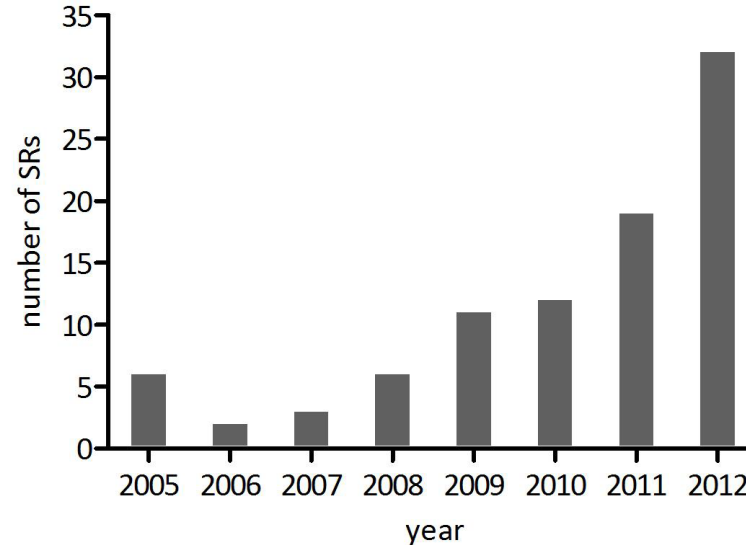
*Less common in translational animal studies*



# SYSTEMATIC REVIEWS OF ANIMAL STUDIES

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The 1<sup>st</sup> systematic review of animal studies performed by Horn et al 2001, Stroke



# HOW TO PERFORM A SYSTEMATIC REVIEW

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- Phrase a specific research question
- Define in- & exclusion criteria
- Search systematically for relevant papers
- Select the relevant papers
- Assess the study quality
- Extract data
- Analyze data (if possible perform a meta-analysis)
- Interpret and present data

# SYSTEMATIC REVIEW OF ANIMAL STUDIES ON STROKE RESEARCH:

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...translational failure in stroke research...

- > 600 drugs tested for efficacy in animal models of focal cerebral ischemia
- 374 drugs positive results in preclinical animal studies
- 97 tested in clinical trials but only 1 drug effective in humans ....

*“Why does everything work in animals  
and nothing works in humans.....”*



# SYSTEMATIC REVIEWS HAS PUT FOCUS ON WHY TRANSLATION IS FAILING

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- Insufficient reporting & poor methodological quality
- Publication bias
- Differences in experimental design
- Biological differences
- .....

# LACK OF BLINDING AND RANDOMIZATION – POOR METHODOLOGICAL QUALITY

*“ the effect of experimenter bias on the performance of the albino rat*

- Maze-bright rats – fast learners
- Maze-dull rats – not too bright
- The maze-bright rats were the best to find the treat
- The maze-bright rats were the cutest, the cleanest
- *However there was no difference in between the to types of rats..!*

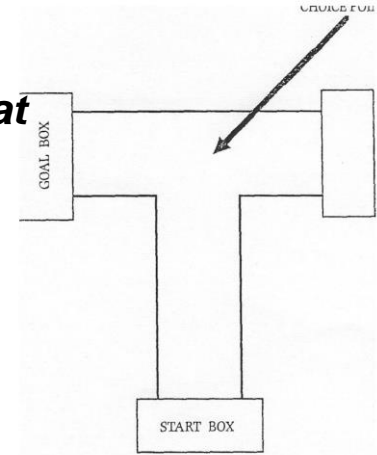


Figure 21.1 Example of a T-maze

# THE EXPERIMENTAL DESIGN & PUBLICATION BIAS

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- Difference in the experimental design of animal studies versus clinical trials
  - e.g. the time point of intervention – e.g. drug/intervention therapy for acute myocardial infarction
- Not reporting negative or neutral results
  - e.g. in stroke 14% (estimated ) of animal studies not reported

# BIOLOGICAL DIFFERENCES

## Selection of animal model



- Effect of pregnancy on vascular function of mesenteric arteries
- Many conflicting results in literature
- Overview of available knowledge
- New insight in selection of animal model

	SDR	WR
- Flow	↑	↑
- Myogenic reactivity	↓	=
- ECM elasticity	↑	=
- Gq <sub>EC</sub> pathway	↑	=
- Gq <sub>SMC</sub> pathway	↓	=
- Gs <sub>SMC</sub> pathway	↑	?
- NO-sensitivity	=	=



## BENEFITS FROM SYSTEMATIC REVIEWS AND META-ANALYSES ?

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- Improved translation
- A more evidence based study design => **Refine** our animal studies
- Eliminate unnecessary duplication => **Reduce** the number of animals used
- Prompts responsible conduction of research
- Transparent translation and a better research quality
- Improve patient safety
- Get value for (funding-) money..

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# THE 17<sup>TH</sup> AND 18<sup>TH</sup> OF NOVEMBER IN AARHUS

## SYMPOSIUM

### Speakers:

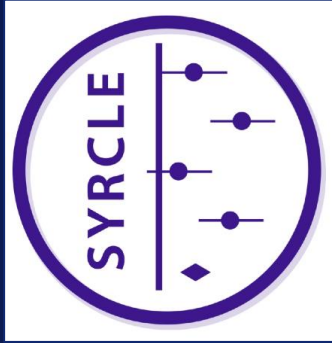
- ✧ Malcolm MacLeod (CAMARADES)
- ✧ Hanna Vesterinen (CAMARADES)
- ✧ Carlijn Hooijmans (SYRCLE)
- ✧ Kim E Wever (SYRCLE)
- ✧ Judith van Luijk (SYRCLE)
- ✧ Gillian Booth (Centre for Reviews and Dissemination)
- ✧ Abstract session (please send in a SR)

STILL ROOM FOR YOU...

## WORKSHOP

- ✧ Identify & select studies
- ✧ Quality assessment
- ✧ Data extraction and metaanalyses

Thank you to:



& for your attention 😊