



# ***Drug development***

## **CLINICAL TRIALS**

**Phase I** : first use in humans  
(usually healthy)

**Phase II** : proof of concept  
surrogate outcome  
safety  
short term effects

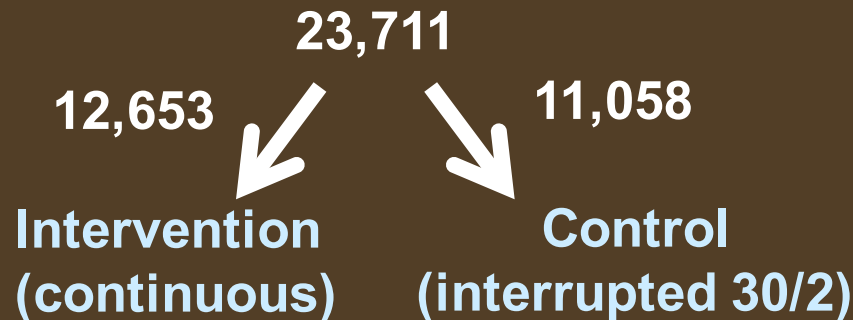
**Phase III** : larger samples  
clinically relevant outcome  
longer term outcomes  
pivotal studies (efficiency)



**Phase IV** : clinical experience, safety

## **Trial of Continuous or Interrupted Chest Compressions during CPR**

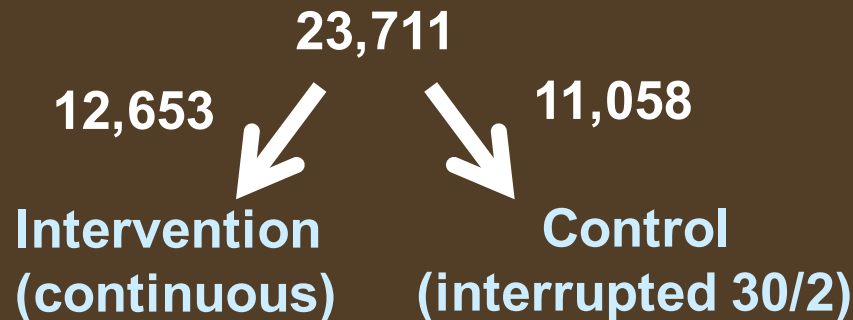
Graham Nichol, M.D., M.P.H., Brian Leroux, Ph.D., Henry Wang, M.D., Clifton W. Callaway, M.D., Ph.D., George Sopko, M.D., Myron Weisfeldt, M.D., Ian Stiell, M.D., Laurie J. Morrison, M.D., Tom P. Aufderheide, M.D., Sheldon Cheskes, M.D., Jim Christenson, M.D., Peter Kudenchuk, M.D., Christian Vaillancourt, M.D., Thomas D. Rea, M.D., Ahamed H. Idris, M.D., Riccardo Colella, D.O., M.P.H., Marshal Isaacs, M.D., Ron Straight, Shannon Stephens, Joe Richardson, Joe Condle, Robert H. Schmicker, M.S., Debra Egan, M.P.H., B.S.N., Susanne May, Ph.D., and Joseph P. Ornato, M.D., for the ROC Investigators\*



<b>Hospital survival</b>	<b>9.0 %</b>	<b>9.7 %</b>	<b>p = 0.07</b>
<b>Favorable neurological outcome</b>	<b>7.0 %</b>	<b>7.7 %</b>	<b>p = 0.09</b>
<b>Hospital- free survival</b>	<b>- 0.2 days</b>		<b>p = 0.004</b>

## Trial of Continuous or Interrupted Chest Compressions during CPR

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**Hospital survival**

**9.0 %**

**9.7 %**

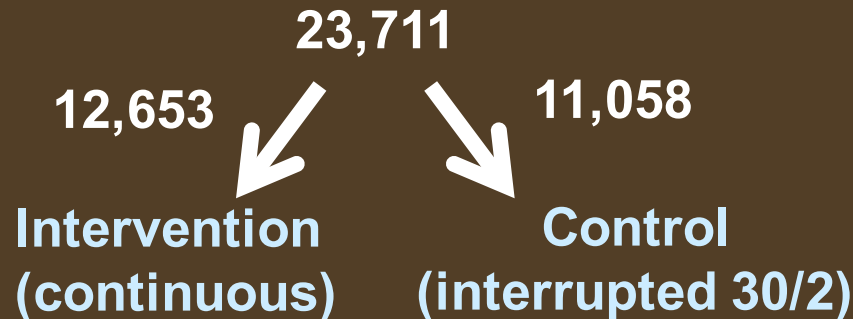
**p = 0.07**

### CONCLUSIONS

In patients with out-of-hospital cardiac arrest, continuous chest compressions during CPR performed by EMS providers did not result in significantly higher rates of survival or favorable neurologic function than did interrupted chest compressions.

## **Trial of Continuous or Interrupted Chest Compressions during CPR**

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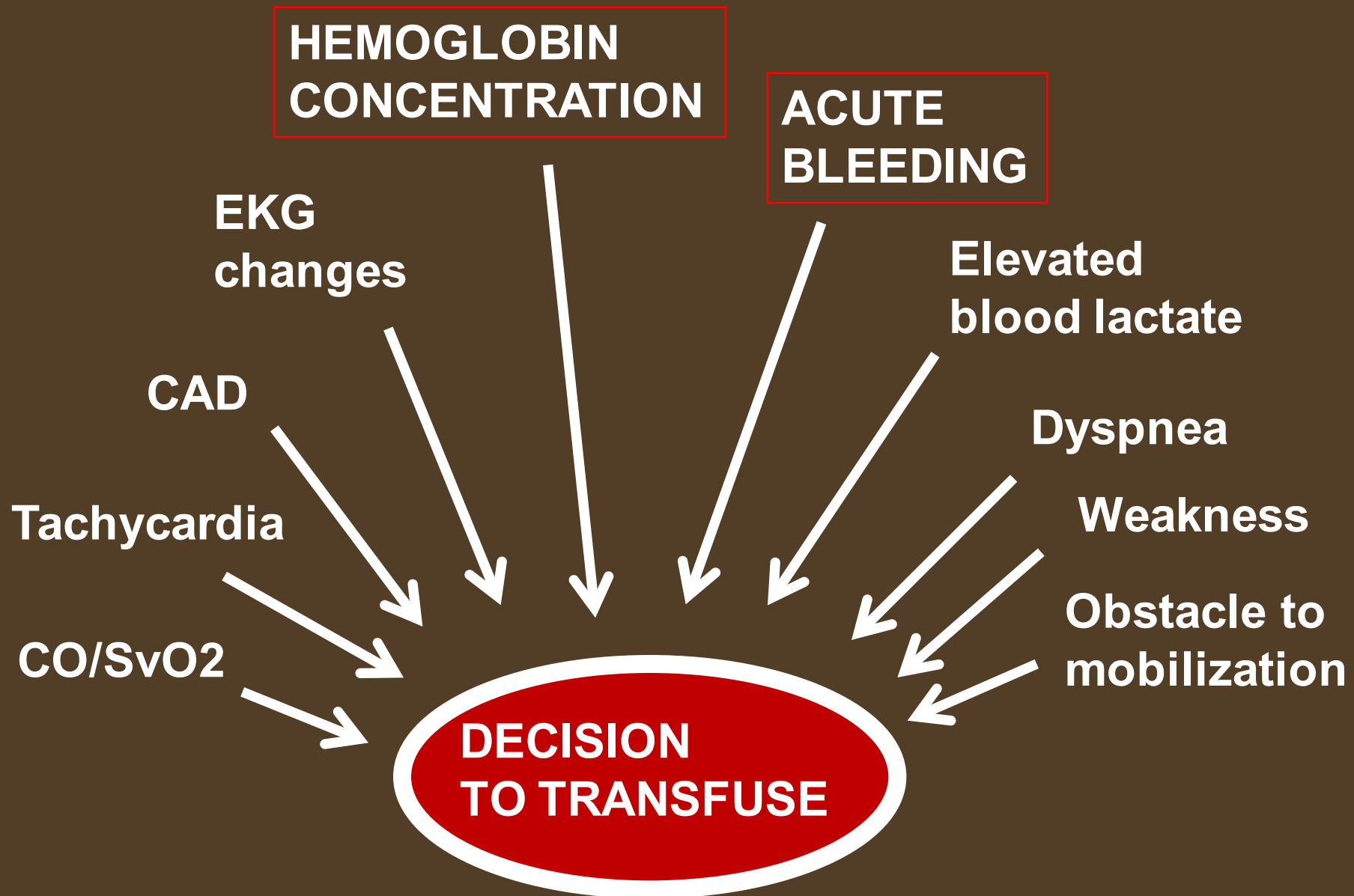


<b>Hospital survival</b>	<b>9.0 %</b>	<b>9.7 %</b>	<b>p = 0.07</b>
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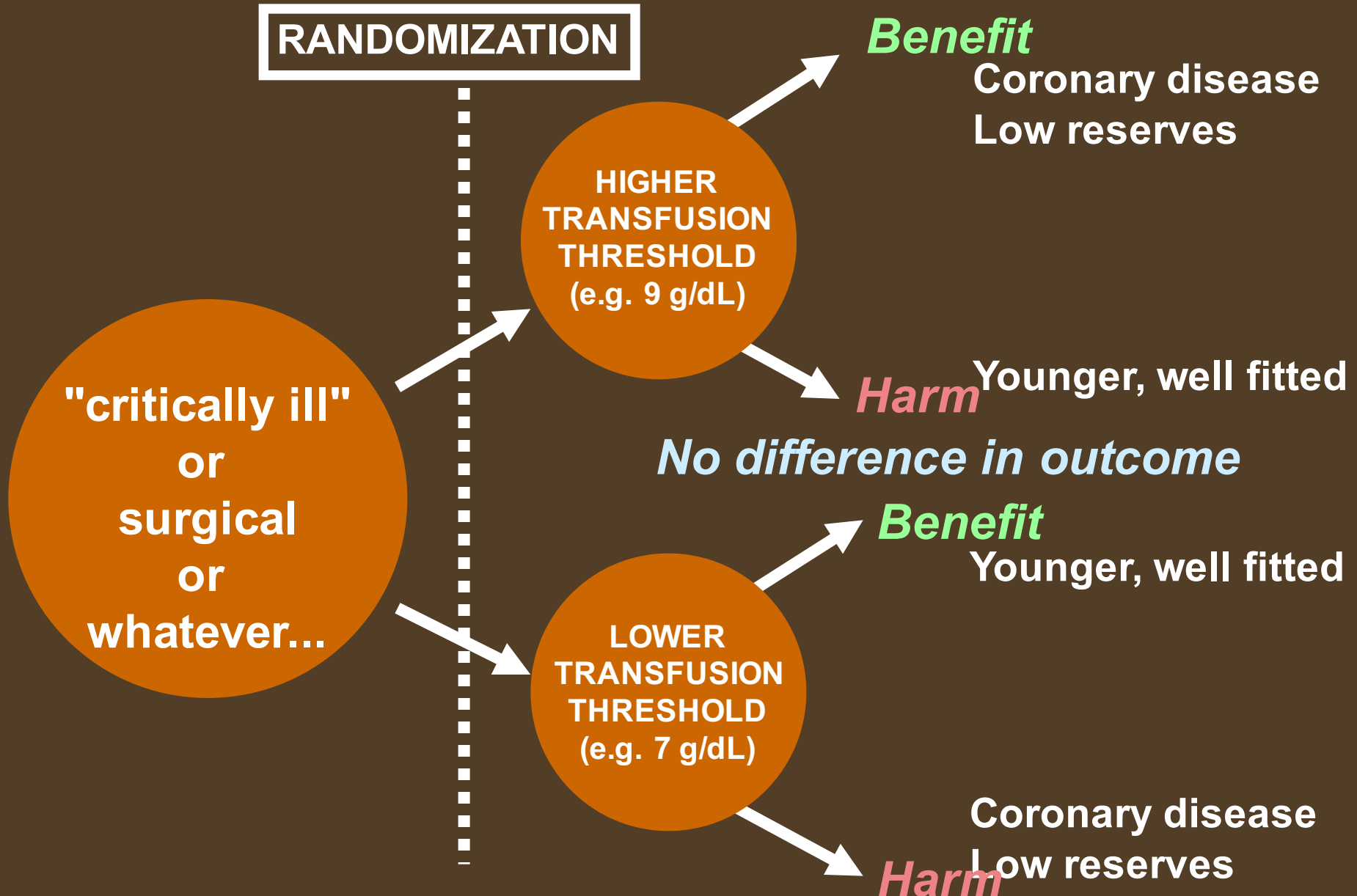
**Their power calculation : total of 23,000 patients for a 1.3% (9.4-8.1%) difference ( $p < 0.05$ ).**

**The difference was only 0.7% (9.7-9.0%) ( $p = 0.07$ ).**  
**To find statistical significance, one would need to multiply the population by about 2 in the two groups**

# When to transfuse



# CLINICAL TRIALS IN THE ICU



# CLINICAL STUDIES IN THE ICU

POPULATION OF INTEREST

POPULATION OF INTEREST

**RCT**

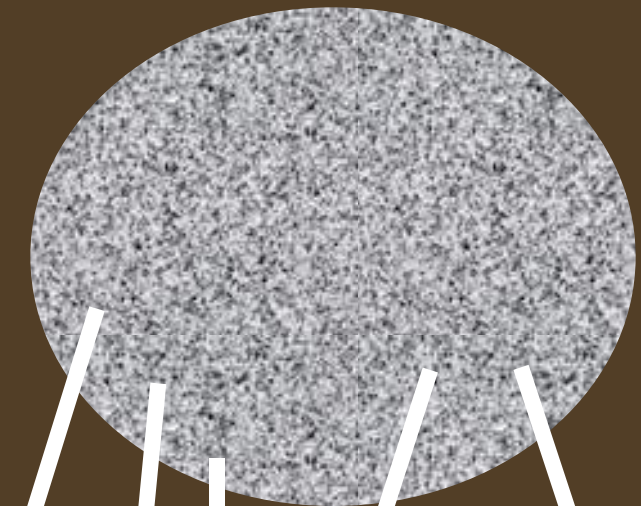


randomization

A

B

No difference ?



Multivariable  
analysis

A

B

Propensity  
matching

**Observational studies**



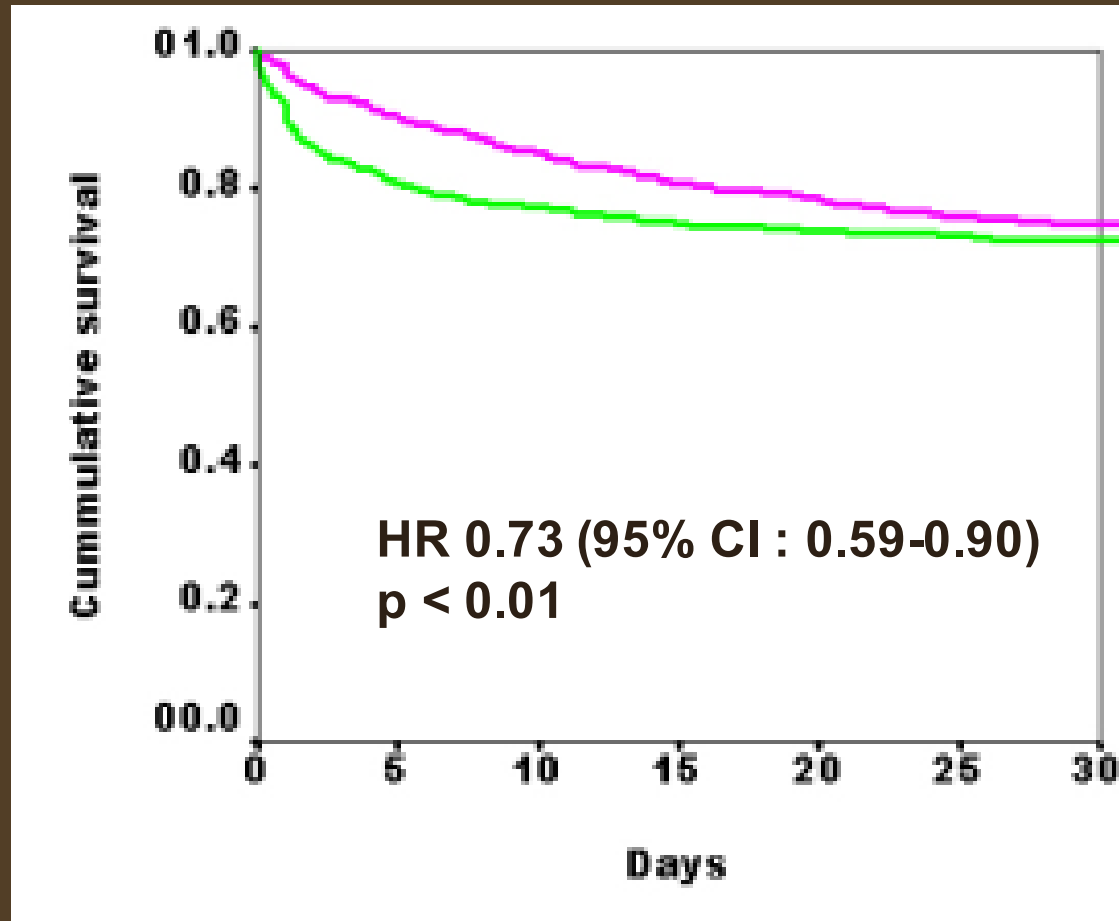
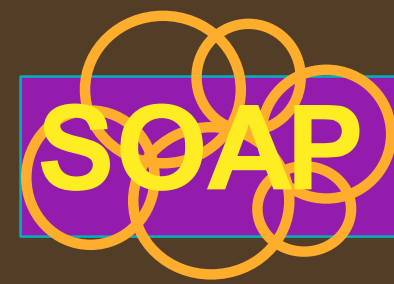
# ASSOCIATION BETWEEN TRANSFUSIONS AND OUTCOMES

**more seriously ill  
more anemic**



**more transfusions → more complications**  
**?** (incl. death)

# BLOOD TRANSFUSIONS



transfusion

N = 821

no transfusion

N = 821

propensity

N = 1642 patients

Anesthesiology 108: 31-9, 2008

# ANIMAL STUDIES

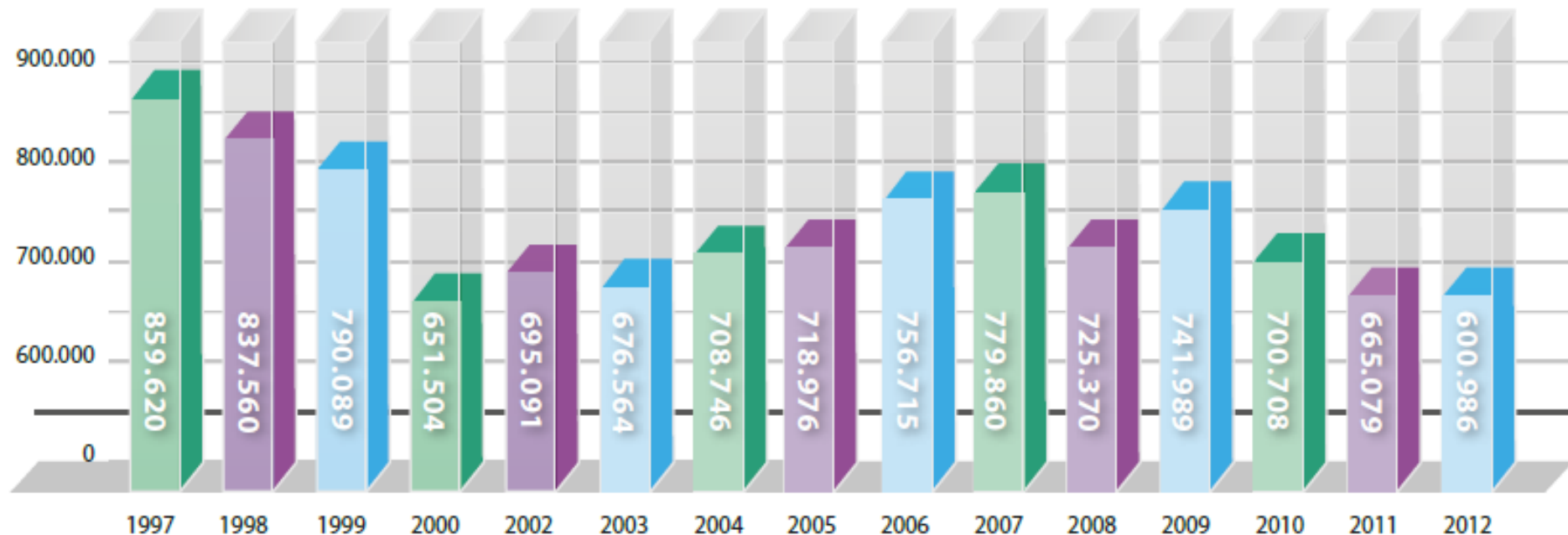
**2003 - Belgium**

**388 authorized laboratories**

**Rodents and rabbits = 93%**

**Fish, reptiles, frogs = 4%**

**Birds = 2%**



# **ANIMAL STUDIES**

## **OPPOSING ARGUMENTS**

- **Violation of animals rights**
  - **Needless suffering**
  - **Inappropriate use**
- when clinical or computer simulation could provide the information**

# **ANIMAL STUDIES**

## **PREREQUISITE**

**Specific scientific question**

**Familiarity with the scientific literature**

**Knowledge of the different models**

**Avoidance of unnecessary suffering**

# ANIMAL STUDIES

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## Laboratory Animal Science

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### Profile

Since 2004, the Faculty of Pharmaceutical, Biomedical and Veterinary Sciences has offered a course in Laboratory Animal Sciences (LAS) for scientists (category C).

This course meets the requirements for recognition as 'Cat C Animal Experiment Leader' as defined by the royal decree of 13 September 2004. This royal decree regulates the education and training of persons performing or participating in animal experiments, and those responsible for the care of laboratory animals.

Very recently, the LAS course offered by the Faculty of Pharmaceutical, Biomedical and Veterinary Sciences also became the first course in Belgium to be accredited by FELASA (the Federation of Laboratory Animal Science Associations). This means that the quality of the programme is internationally recognised and is constantly monitored and evaluated. This also means that, with a certificate from the University of Antwerp, you can perform research in countries other than the one in which you trained, i.e. Belgium.

# **ANIMAL STUDIES**

## **ADVANTAGES**

**Evaluation of efficacy / toxicity**

**Homogeneity of the subjects**

**No co-morbidity (unless desired)**

**Controlled timing of interventions**

**Possibility of pretreatment**

## **ANIMAL STUDIES**

## **LIMITATIONS**

**Different physiology than humans**

**Healthy or diseased ?**

**Young / no arteriosclerosis**

**Insensitive / Resistant**



# **ANIMAL STUDIES**

## **MODELS**

**Healthy or diseased animals**

**As clinically relevant as possible**

**Ethics committee approval**

# **ANIMAL STUDIES**

## **SPECIES**

**Logistic / financial**

**Emotional / legal considerations**

**Horses**

**Primates**

**ANIMAL STUDIES**

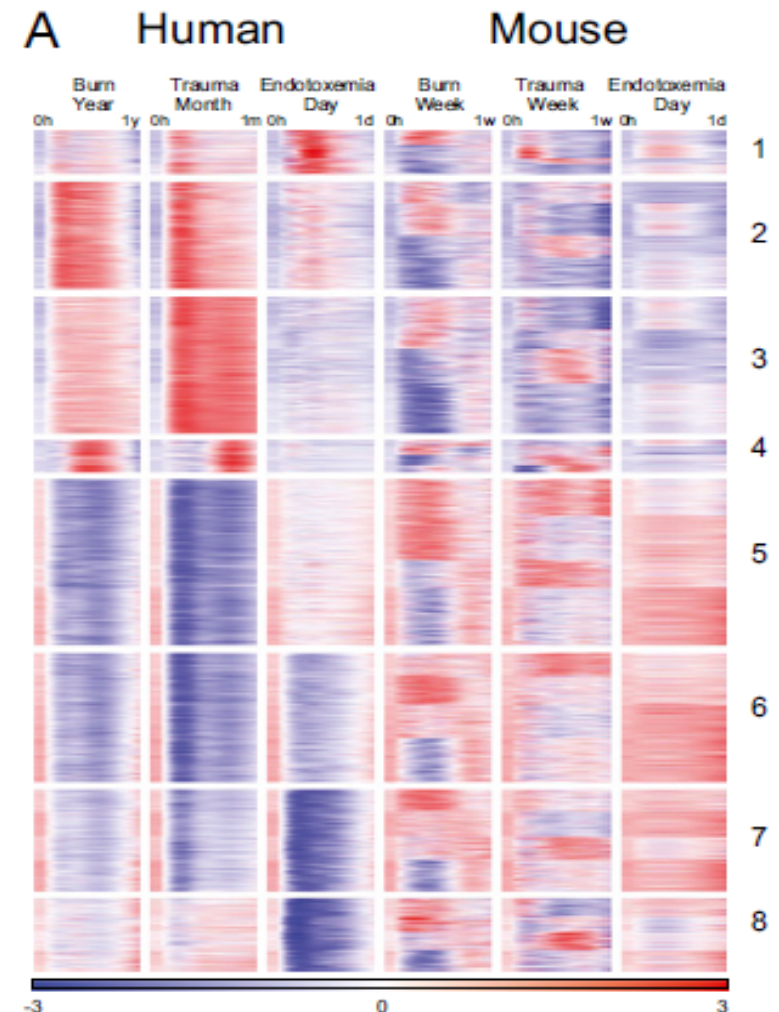
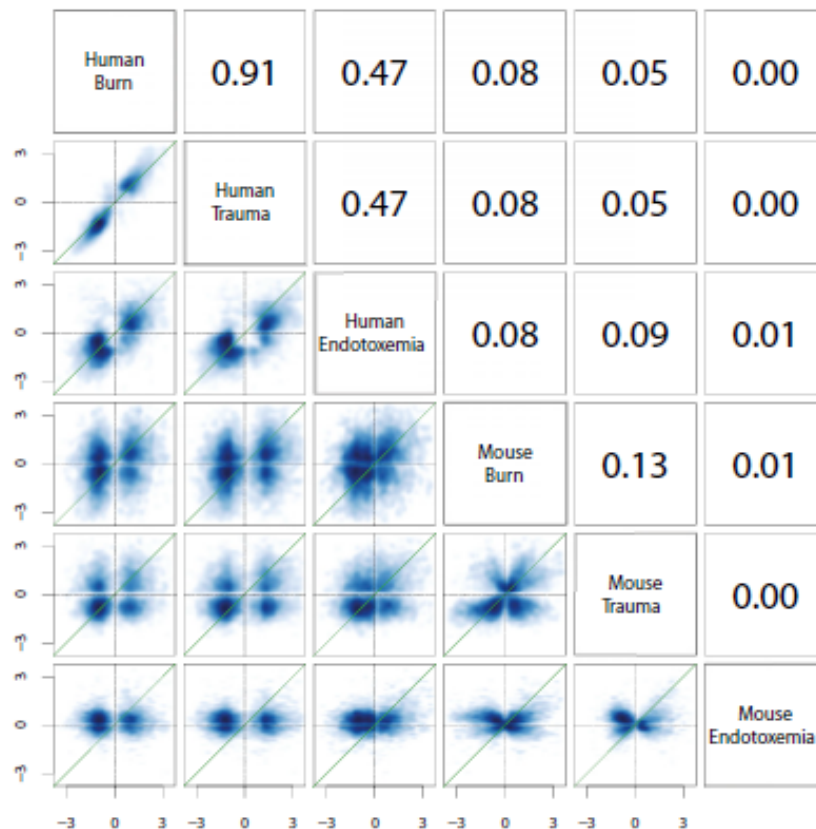
**SPECIES**

**Rodents**

# Genomic responses in mouse models poorly mimic human inflammatory diseases

Junhee Seok<sup>a,1</sup>, H. Shaw Warren<sup>b,1</sup>, Alex G. Cuenca<sup>c,1</sup>, Michael N. Mindrinos<sup>a</sup>, Henry V. Baker<sup>c</sup>, Weihong Xu<sup>a</sup>, Daniel R. Richards<sup>d</sup>, Grace P. McDonald-Smith<sup>e</sup>, Hong Gao<sup>a</sup>, Laura Hennessy<sup>f</sup>, Celeste C. Finnerty<sup>g</sup>, Cecilia M. López<sup>c</sup>, Shari Honari<sup>f</sup>, Ernest E. Moore<sup>h</sup>, Joseph P. Minei<sup>i</sup>, Joseph Cuschieri<sup>j</sup>, Paul E. Bankey<sup>k</sup>, Jeffrey L. Johnson<sup>h</sup>, Jason Sperry<sup>l</sup>, Avery B. Nathens<sup>m</sup>, Timothy R. Billiar<sup>l</sup>, Michael A. West<sup>n</sup>, Marc G. Jeschke<sup>o</sup>, Matthew B. Klein<sup>l</sup>, Richard L. Gamelli<sup>p</sup>, Nicole S. Gibran<sup>l</sup>, Bernard H. Brownstein<sup>q</sup>, Carol Miller-Graziano<sup>k</sup>, Steve E. Calvano<sup>r</sup>, Philip H. Mason<sup>e</sup>, J. Perren Cobb<sup>s</sup>, Laurence G. Rahme<sup>t</sup>, Stephen F. Lowry<sup>c,2</sup>, Ronald V. Maier<sup>l</sup>, Lyle L. Moldawer<sup>c</sup>, David N. Herndon<sup>g</sup>, Ronald W. Davis<sup>a,3</sup>, Wenzhong Xiao<sup>a,t,3</sup>, Ronald G. Tompkins<sup>t,3</sup>, and the Inflammation and Host Response to Injury, Large Scale Collaborative Research Program<sup>4</sup>

PNAS | February 26, 2013



## Review Article

### ABANDON THE MOUSE RESEARCH SHIP? NOT JUST YET!

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Ansgar O. Aasen,<sup>||</sup> Mayuki Aibiki,<sup>¶</sup> Luciano C. Azevedo,<sup>\*\*</sup> Soheyl Bahrami,\*  
Mihaly Boros,<sup>††</sup> Robert Cooney,<sup>‡‡</sup> Salvatore Cuzzocrea,<sup>§§</sup> Yong Jiang,<sup>|||</sup>  
Wolfgang G. Junger,<sup>¶¶</sup> Hiroyuki Hirasawa,<sup>\*\*\*</sup> Richard S. Hotchkiss,<sup>†††</sup>  
Xiang-An Li,<sup>‡‡‡</sup> Peter Radermacher,<sup>§§§</sup> Heinz Redl,\* Reinaldo Salomao,<sup>||||</sup>  
Amin Soebandrio,<sup>¶¶¶</sup> Christoph Thiemermann,<sup>\*\*\*\*</sup> Jean-Louis Vincent,<sup>††††</sup>  
Peter Ward,<sup>‡‡‡‡</sup> Yong-Ming Yao,<sup>§§§§</sup> Huang-Ping Yu,<sup>||||||</sup> Basilia Zingarelli,<sup>¶¶¶¶</sup>  
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# **ANIMAL STUDIES**

## **SPECIES**

**Rodents**

**Rabbits**

**Dogs & cats**

**Pigs**

**Sheep**

**Primates**

## **ANIMAL STUDIES**

## **SEPSIS MODELS**

- **Endotoxin administration**
- **Infusion of live organisms**
- **Peritonitis (CLP)**
- **Pneumonia**

# **ANIMAL STUDIES**

## **PROTOCOL**

- ❖ **Power calculation ?**
- ❖ **Randomisation**
- ❖ **Blinding ?**
- ❖ **Duration of observation**
- ❖ **Effects of anesthesia**
- ❖ **Ethics committee approval**



# **ANIMAL STUDIES**

## **QUALIFICATIONS**

- ✓ **Accredited lab**
- ✓ **Veterinary doctor available at all times**
- ✓ **Trained responsible person**
- ✓ **Recording of animals used**