

“Of animals and men:  
differences between species  
and their impact on research“

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# Molecular Compatibility

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## *Clinical Liver-Xenotransplantation*

	<b>man</b> (normal)	<b>baboon</b> (normal)	<b>patient</b> (45 d p. op)
Albumine (g/l)	40 – 50	20 – 40	19
Total proteine (g/l)	60 - 84	40 – 60	40
Cholesterole (mmol/l)	3.1 – 5.7	1.03	1.71
Uric acid (mmol/l)	180 – 420	<30	<30

*Starzl et al., The Lancet, 1993*

# Molecular Compatibility

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*Clinical follow-up: haemorrhage*

<b>day p. op</b>	<b>localisation</b>	<b>cause</b>
24	haemothorax	biopsy
27 – 39	gastro-intestinale	esophagitis duodenitis
61	DIC	???
70	sub-arachnoid	aspergillosis

*Starzl et al., The Lancet, 1993*



Horses  
Donkeys  
Mule  
Hinnies

Cats  
Dogs  
Ferrets  
Other carnivora

Mice  
Rats  
Guinea pigs  
Hamsters  
Gerbils  
Rabbits  
Other rodents

Pigs  
Goats  
Sheep  
Cattle

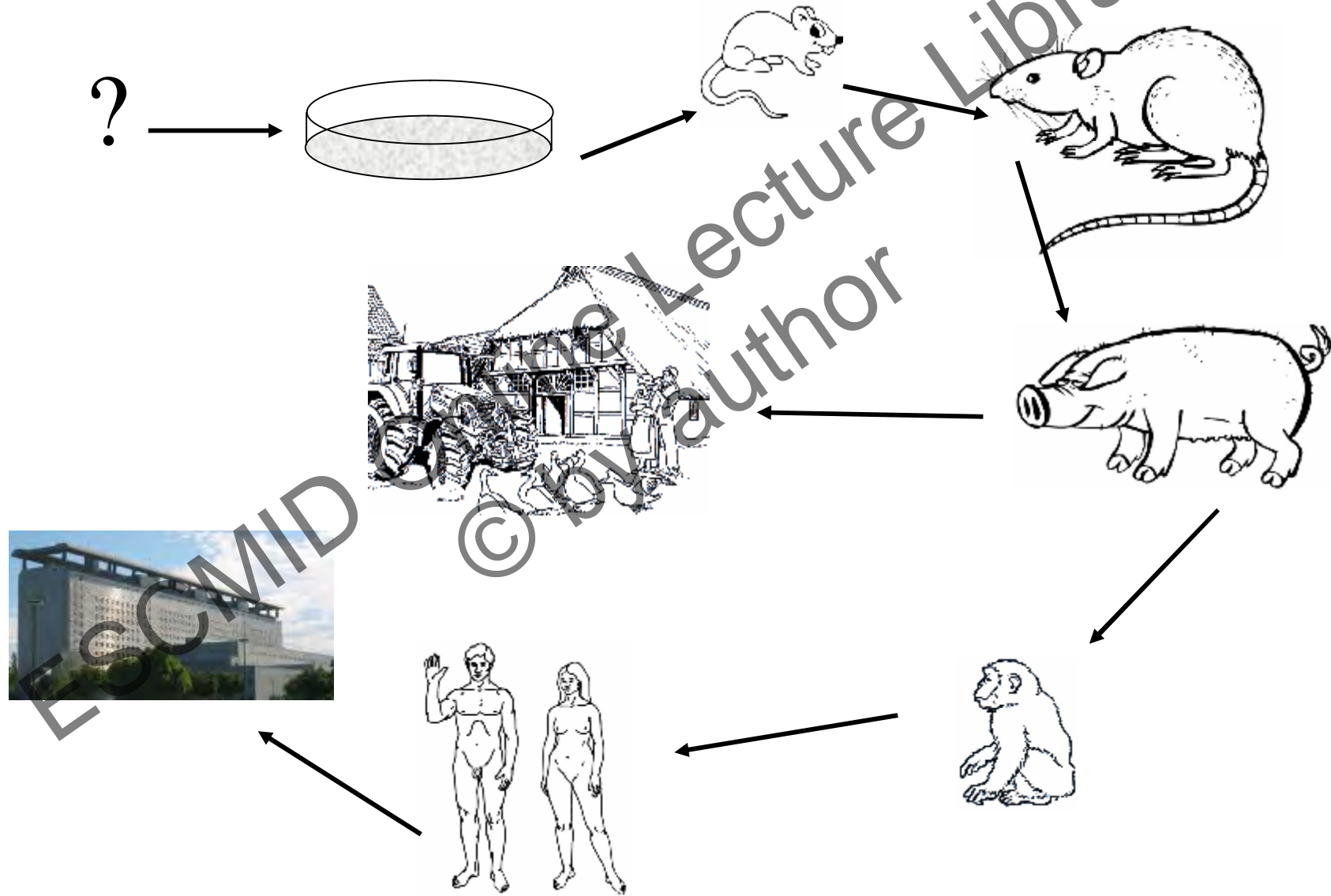
Prosimians  
New-world monkeys  
Old-world monkeys  
Human primates  
Other Mammals

Quails  
Other birds  
Reptiles  
Amphibians  
Fish

1502

# Animals in Research

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# TGN1412

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TGN1412 = anti-human-CD28-antibody  
intended use: e.g. multiple sclerosis

- Tested in mice: no side-effects
- Tested in two different primate-species: no side-effects
- Tested in six male volunteers with 1/500 of primate dosage

side-effects within 5 min  $\Longrightarrow$  cytokine-burst  $\Longrightarrow$  SIRS

$\Longrightarrow$  multiple organ failure  $\Longrightarrow$  ICU

$\Longrightarrow$  long-term damages

# Some Comparisons

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Parameter	Mouse	Pig	Baboon	Man
Body weight (kg)	0.025	300	up to 35	70
Temperature (°C)	36.5 – 38	39.5	36.5	36.5
Heart-rate (beats/min)	600	70	180	70
MAP (mmHg)	110	90	90	80
Glucose (mg/dl)	124 - 262	90	85	100

# Circulatory System of Pig and Man

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	Pig (BW 70kg)	Mensch
SV (ml/beat)	80	70
HR (beats/min)	70	70
CO (ml/min/kg)	80	70
O <sub>2</sub> -Cap. (ml O <sub>2</sub> /l)	220	200
Blood Volume (ml/kg)	7	7
sys. Resist. (dyn/s/cm <sup>-5</sup> )	2.750	1.200
pulm. Resist. (dyn/s/cm <sup>-5</sup> )	120	440



# Kidneys of Pig and Man

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	<b>Pig</b>	<b>Man</b>
Nephrons (n)	$1 \times 10^6$	$1 \times 10^6$
Nephr. + Loop of Henle (%)	3	14
Renal Blood Flow (ml/min)	420	620
Primary Urine (L/d)	140	170
Urine (ml/kg/d)	30	20

# Urine of Pig and Man

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	<b>Pig</b>	<b>Man</b>
pH	5 - 8	5.6 - 7
Ca (mmol/d)	7.5	2.5 – 11.5
P (mmol/d)	33	20 - 45
CL (mmol/d)	200	120 - 240
Na (mmol/d)	13	100 - 150
K (mmol/d)	270	60 – 80
Creatinine (mmol/d)	40	0.8 – 1.7
Protein (mg/l)	-300	-80

# Are there consequences?

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Xeno-transplantation is the transfer of organs between different species

## IXA-directive:

Before introduction of xeno-transplantation into the clinic, experiments have to be conducted in which:

- at least 10 baboons survive for 3 months or more with a porcine heart
- 3-month-survival is at least 60%
- immunosuppression is identical in all animals
- rejection can be suppressed or treated

## Comparison of Baboon and Pig

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	Baboon	Pig (20kg)
Stroke-volume (ml)	22	24
Heart-rate (/min)	165 – 240	90 - 120
O <sub>2</sub> -Capacity (ml O <sub>2</sub> /l)	150	220
2,3-DPG (μmol/g Hb)	16	32
Fe (μg/dl)	55	140
Transferrin (mg/ml)	2.7	5.9
O <sub>2</sub> -Consumpt. (ml/min/kg)	6.7	6.5
O <sub>2</sub> -Extract.-rate crit. (%)	50	57

# Systemic O<sub>2</sub> -supply

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	HR	SV	CO
<b>Baboon</b>	195	x 22 ml	= 4290 ml/min
<b>Pig</b>	110	x 24 ml	= 2640 ml/min

	CO	O <sub>2</sub> -Cap.	O <sub>2</sub> -supply
<b>Baboon</b>	4.29 l/min	x 150 ml O <sub>2</sub> /l	= 643.5 ml O <sub>2</sub> /min
<b>Pig</b>	2.64 l/min	x 220 ml O <sub>2</sub> /l	= 580.3 ml O <sub>2</sub> /min

	O <sub>2</sub> -Consumpt.	O <sub>2</sub> -ER
<b>Baboon</b>	6.7 ml/min/kg =	21%
<b>Pig</b>	6.5 ml/min/kg =	22%

# Systemic O<sub>2</sub>-supply after HTX

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<b>CO</b> (pig)		<b>O<sub>2</sub>-Cap.</b> (baboon)		<b>O<sub>2</sub>-supply</b>
2.64 l/min	x	150 ml O <sub>2</sub> /l	=	396 ml O <sub>2</sub> /min (643.5 before)

**O<sub>2</sub>-Difference**  
247.5 ml O<sub>2</sub>/min (38%)

**O<sub>2</sub>-ER**  
34%

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# Myocardial O<sub>2</sub>–supply after HTX

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## before HTX

	<b>MBF</b>		<b>myoc. O<sub>2</sub>-supply</b>		<b>mO<sub>2</sub>-consump.</b>
<b>Baboon</b>	1.6 ml/min/g	=	0.24 ml O <sub>2</sub> /min/g		0.10 ml/min/g
<b>Pig</b>	0.9 ml/min/g	=	0.20 ml O <sub>2</sub> /min/g		

## after HTX

**MBF (pig)** 0.9 ml/min/g = **mO<sub>2</sub>-supply. (baboon)** **0.13 ml O<sub>2</sub>/min/g**  $\longrightarrow$  **O<sub>2</sub>-ER** 77%

**HR**  
163

**Diastole**  
0.3 sec  $\longrightarrow$  0.12 sec

# But!

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	Baboon	Pig (70 kg)	Man
SV (ml/beat)	22	approx. 80	70
HR (beats/min)	165 – 240	70 – 80	60 - 90
O <sub>2</sub> -Cap. (ml O <sub>2</sub> /l)	150	220	200
2,3-DPG (μmol/g Hb)	16	32	34
Fe (μg/dl)	55	140	110
Transferrin (mg/ml)	2.7	5.9	3.09
VO <sub>2</sub> (ml/min/kg)	6.7	6.5	7



# Species and Drugs

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## Dosage of Xylazine

- Cattle 0.05 mg/kg = 1.0 ml/500kg
- Horse 1.0 mg/kg = 20 ml/500kg

LD<sub>50</sub> of Phenol: cat = 30 mg/kg  
dog = 150 mg/kg

## Rabbits:

- approx. 30% possess atropine-esterase  $\implies$  no effects of atropine
- Gentamycin is neuro-toxic
- Neomycin and Streptomycin are oto-toxic
- Penicillin G causes sterile abscesses

## Dogs:

Ibuprofen causes gastric ulcers even in low dosages

# Some Specialities

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## Pigs:

- physiologic, juvenile anaemia (Hct approx. 22%)
- malignant hyperthermia (up to 95% in some strains)
- vulnerable myocardium

## Dogs:

- collateralisation of myocardium  $\implies$  induction of ischemia is difficult

## Rabbits:

- coprophagy  $\implies$  oral antibiotics could be life-threatening
- very touchy  $\implies$  no experiments in the summer

## Guinea pigs:

- can not store vitamin C  $\implies$  necessity of addition to diet

# Mice and Infectious Agents

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<b>germ</b>	<b>tropism</b>	<b>influence (e.g.)</b>
Sendai virus	respiratory system	function of WBC, synthesis of cytokines + chemokines, apoptosis
Parvo virus	intestine, liver, pancreas	direct influence on T-cells, T-cell-dysfunction
Mycopl. pulm.	nasopharynx middle ear	pulmonary immunity, altered T-cells
Salmonella spp.	intestine, liver, blood vessels	increased cytokine synthesis, expression of CD62E on endothelium expression of CD11b, CD18 on neutrophils

# Susceptibility of different mouse strains

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agent	strain				
	C57BL/6	C3h	Balb/c	C3H/He	DBA/2
Sendai Virus	---	+	+	+	+++
Ectromelia Virus	---	+++	+++	+	+
Streptobac. mon.	+++	+	---	---	+

# Summary and Perspective

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- Differences between species exist, not only in regard of bodyweight and size but as well in
  - physiology
  - pharmacology
  - microbiology
- These differences might have an impact on research
- Thus, optimal information on the model and its specific characteristics should be gathered before experiments are conducted