Ansätze zur Neuroprotektion bei Neugeborenen

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Jahresversammlung der
Niedersächsischen Perinatalerhebung (NPR)
7. Februar 2020

Universitätsklinikum Essen

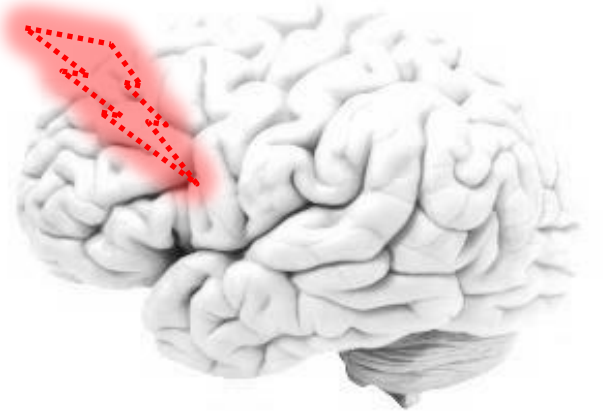
.....keine Interessenkonflikte....

Ursachen der perinatalen Hirnschädigung

Inflammation

Hyperoxie

Hypoxie-Ischämie



Medikamente

Plazentainsuffizienz

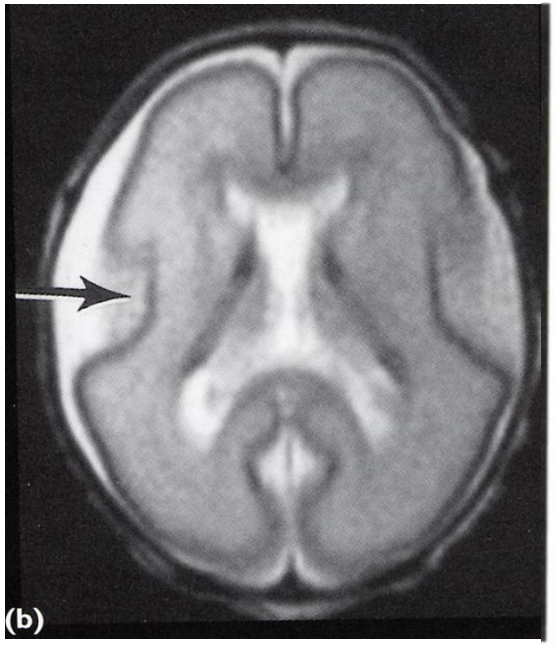
Trauma

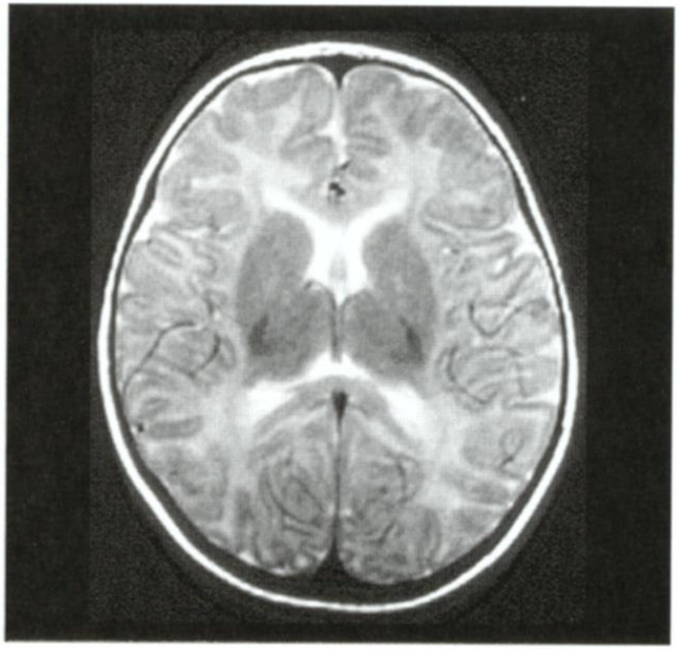
Blutungen

Neuroprotektion bei Frühgeborenen

- **Mechanismen**
- Neuroprotektive Strategien
  - *Erythropoietin (EPO)*
  - *jenseits von EPO*

Gehirnentwicklung im letzten Trimester und mit 2 Jahren

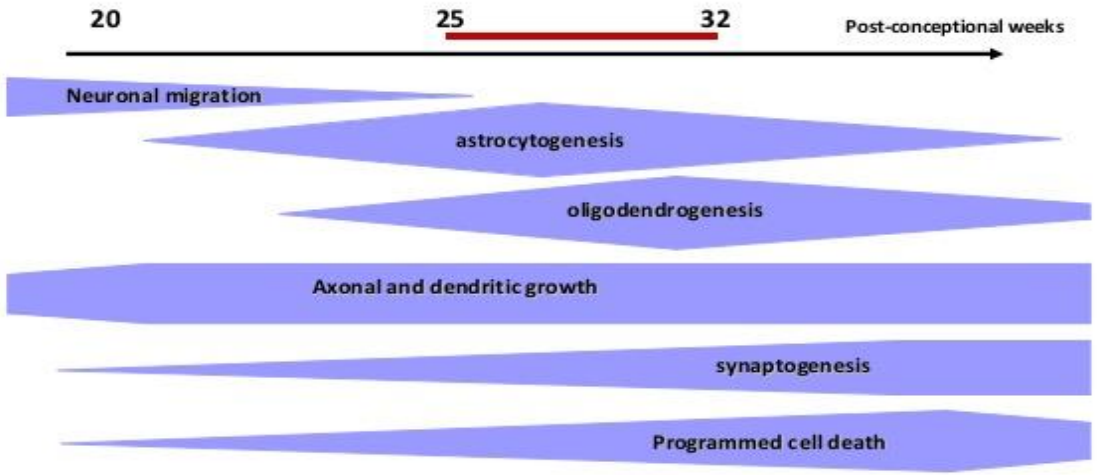




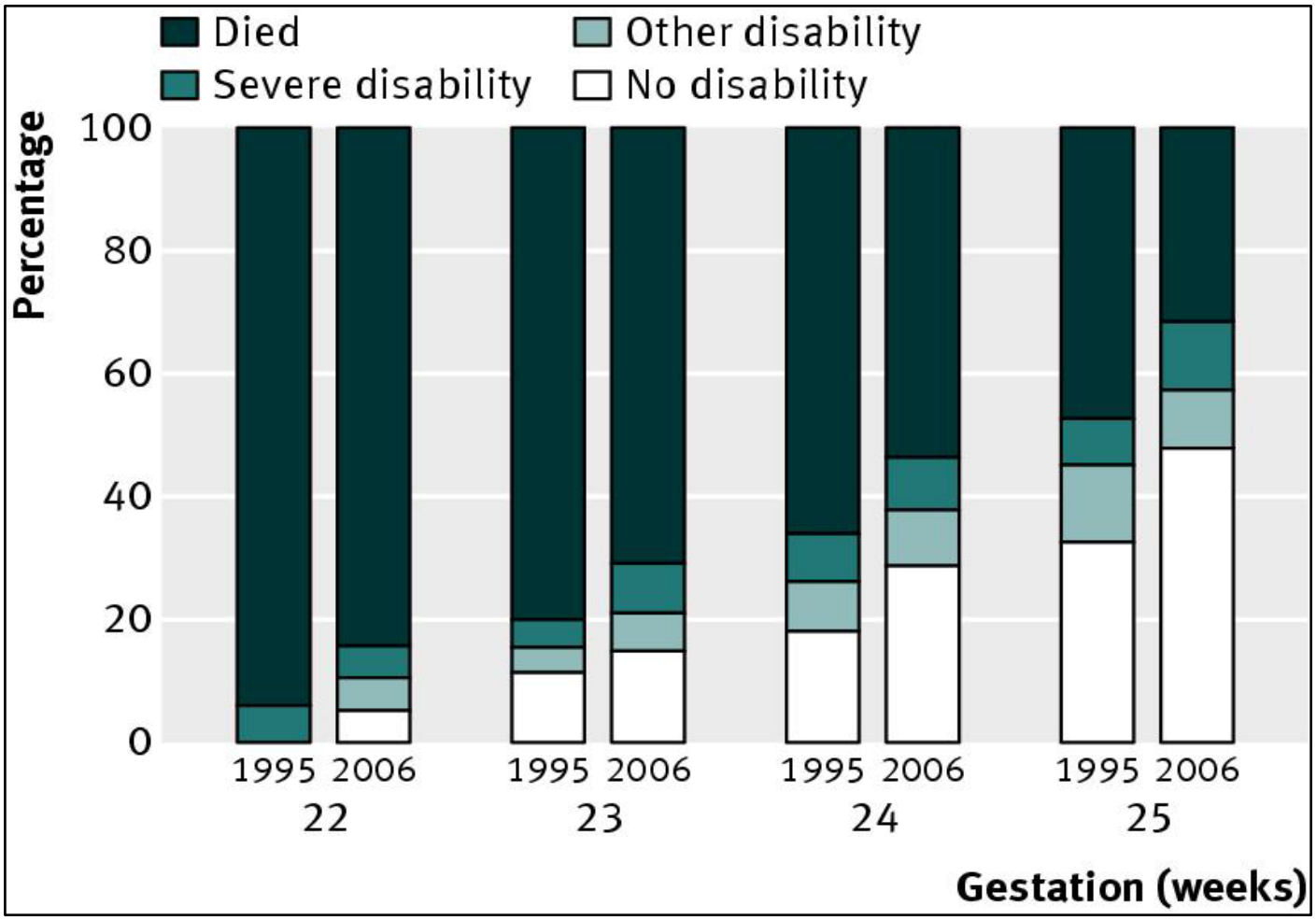
25 SSW

am ET

24 Monate



Die Epicure Studien (1995 and 2006)



Marlow et al BMJ 2012

Die Inzidenz der zystischen PVL geht zurück

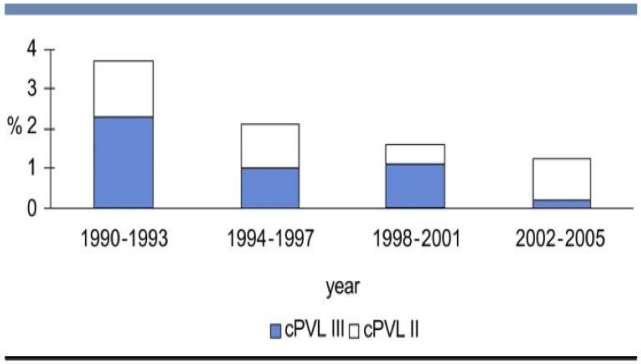


Figure 4. C-PVL grade II and III within total cohort.

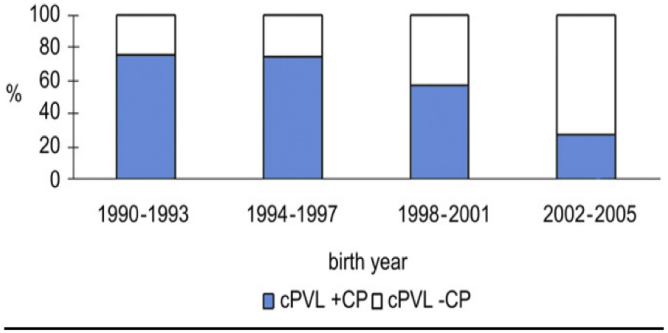
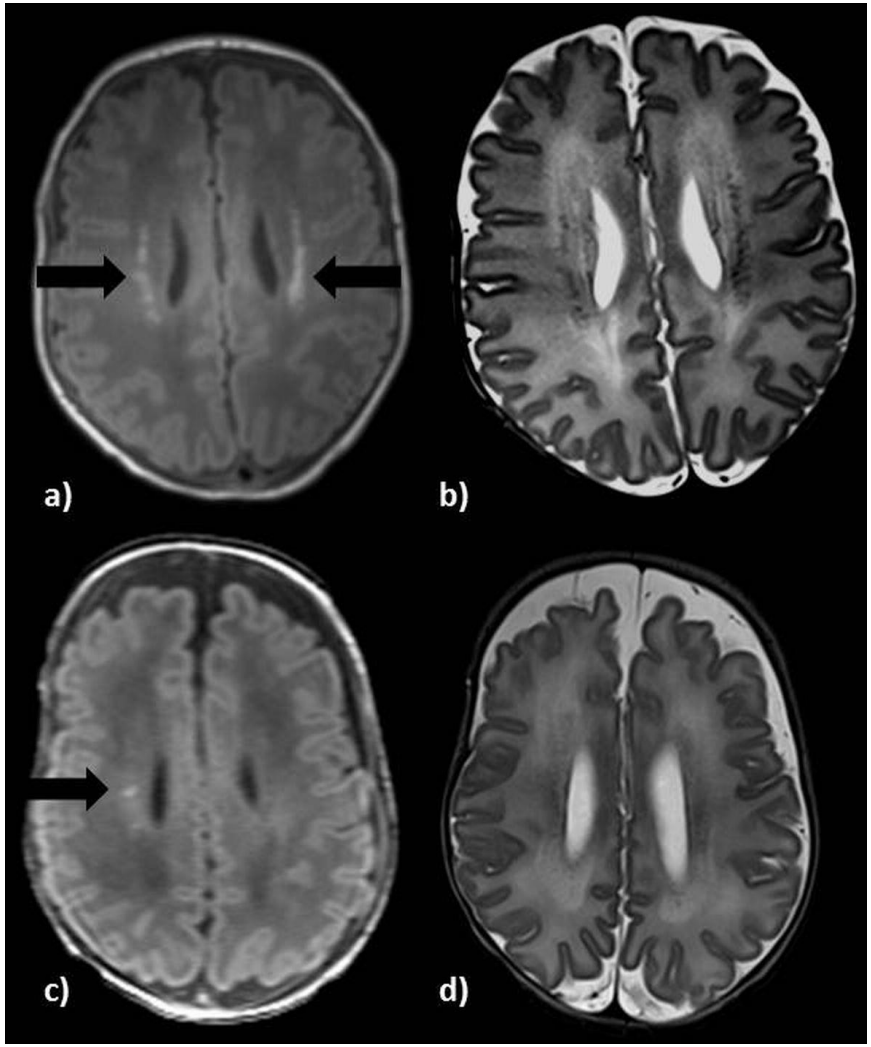


Figure 3. C-PVL in relation to CP.

n=3287, GA <34 SSW, 1990-2005

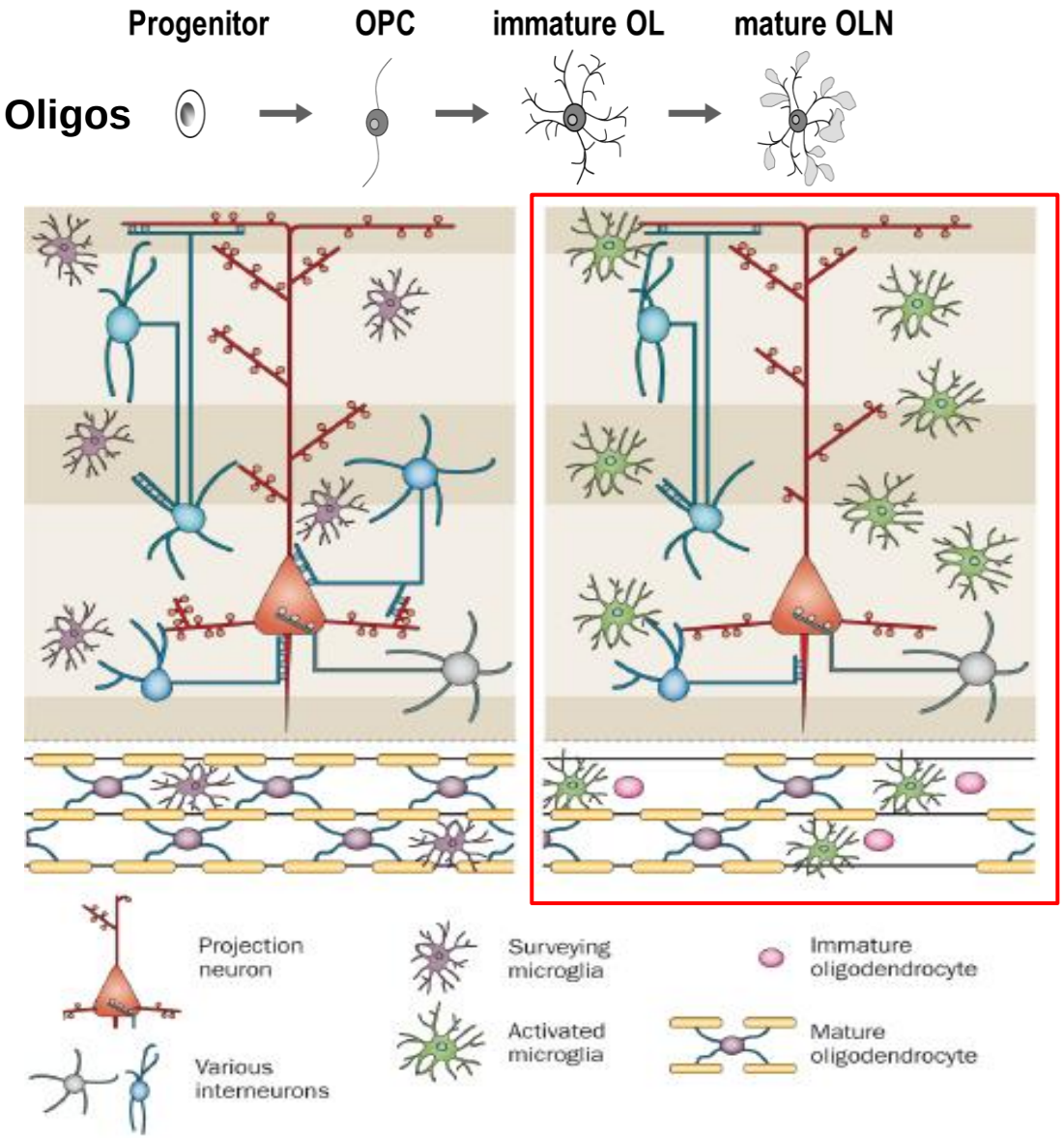


UK Essen Kohorte

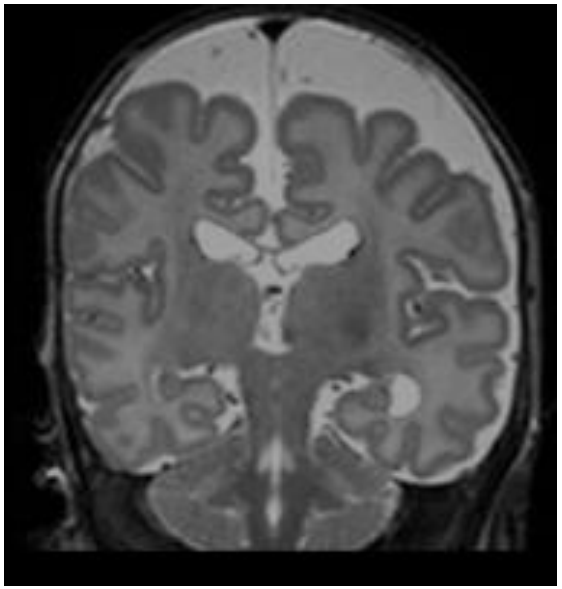
van Haastert et al., J of Pediatr 2011,

Sellier E, …., Krägeloh-Mann et al. for the Surveillance of Cerebral Palsy Network, Dev Med Child Neurol 2016

Preterm phenotype- Encephalopathy of prematurity

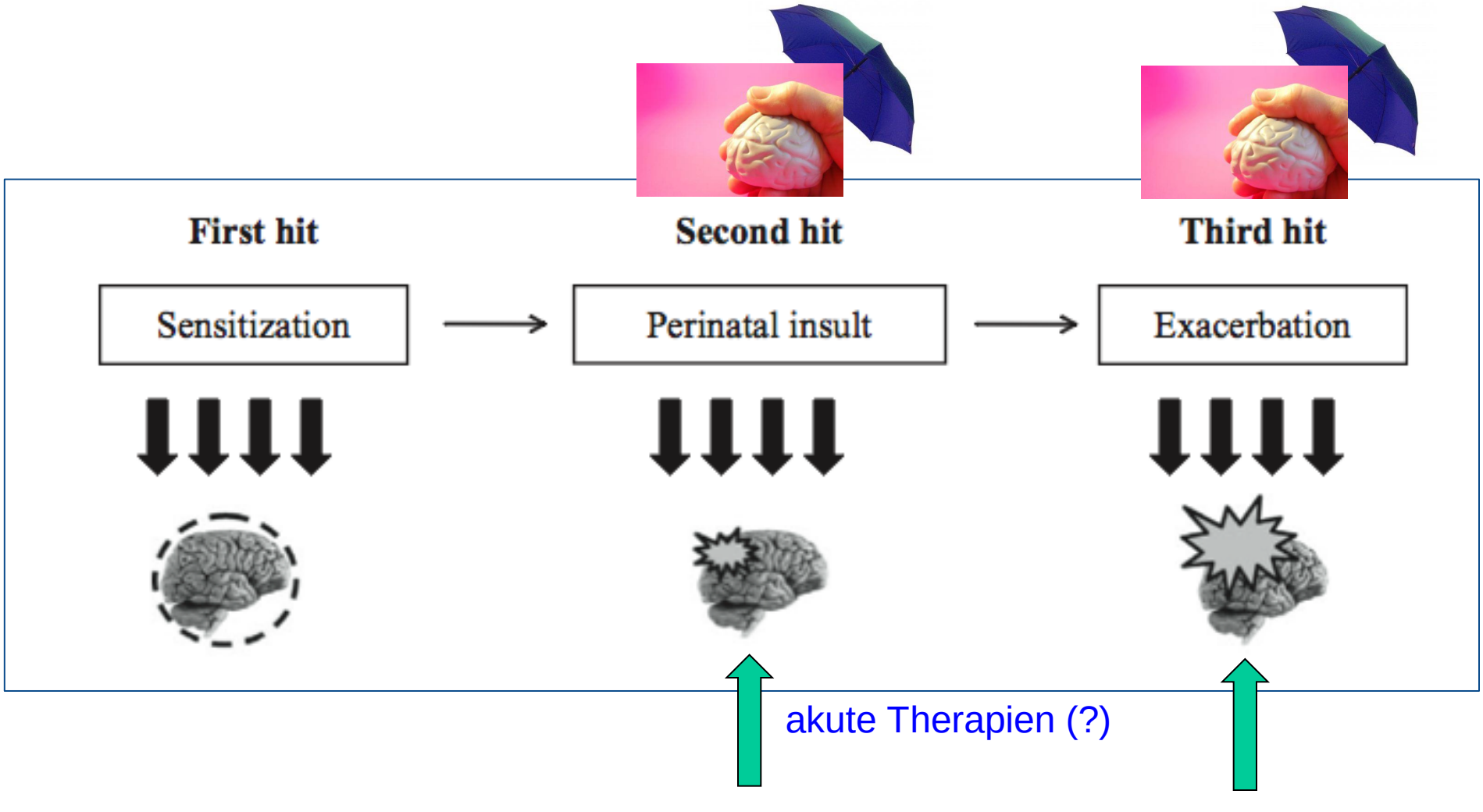


- Pathologie der weißen Substanz
- kortikale Reduktion
- Ventrikulomegalie



Hagberg et al. Nat Rev Neurol 2015

Die „multiple hit“ Hypothese

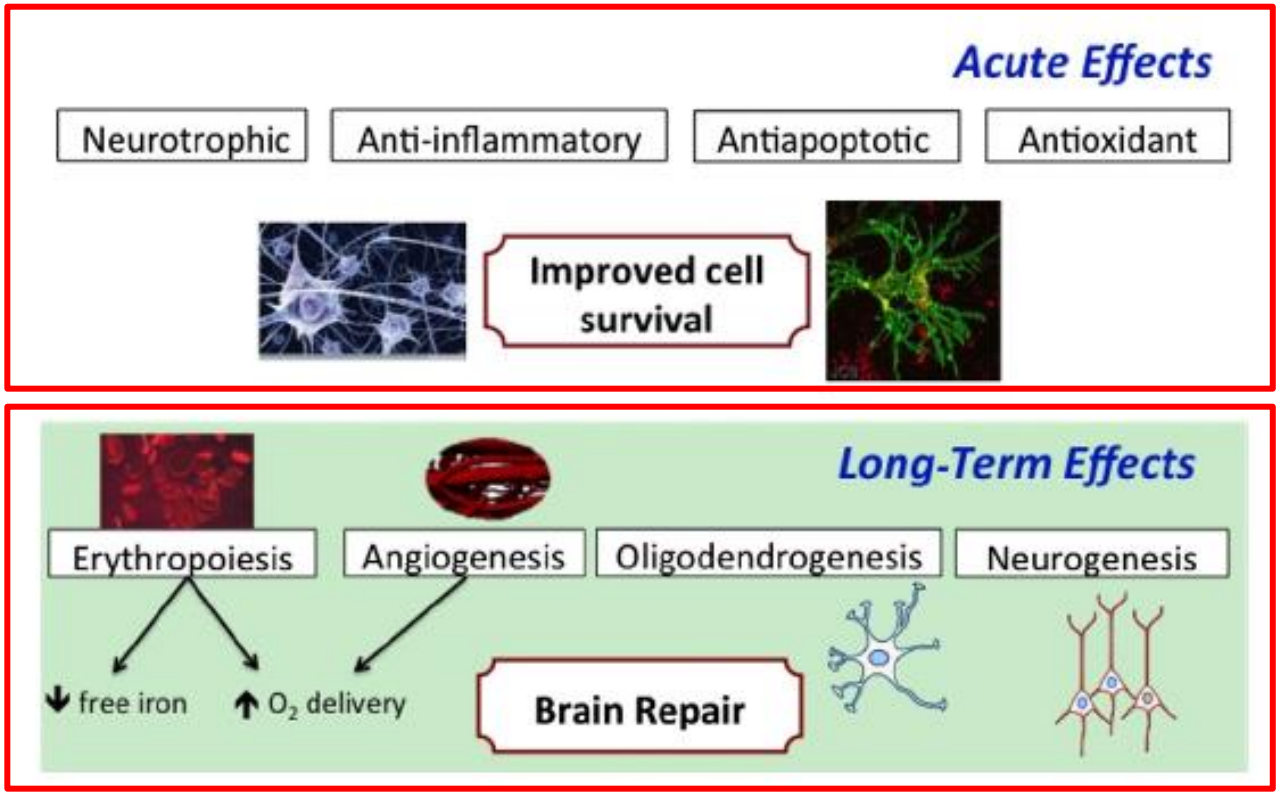


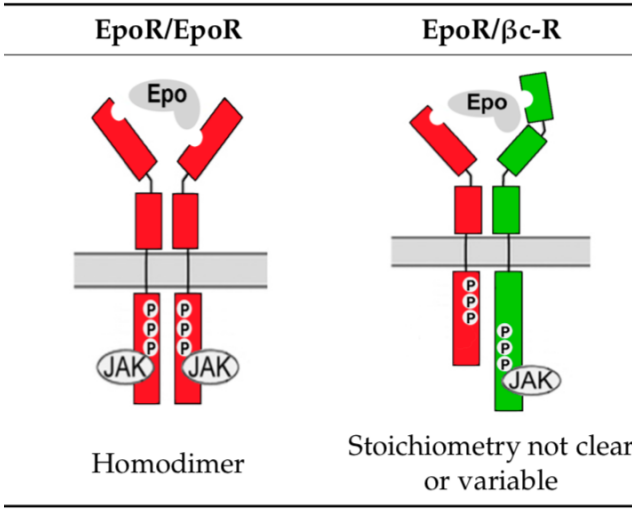
Dammann et al. Biol Neonat 2004 (for review)
Kaindl et al. J Child Neurol 2009 (for review)

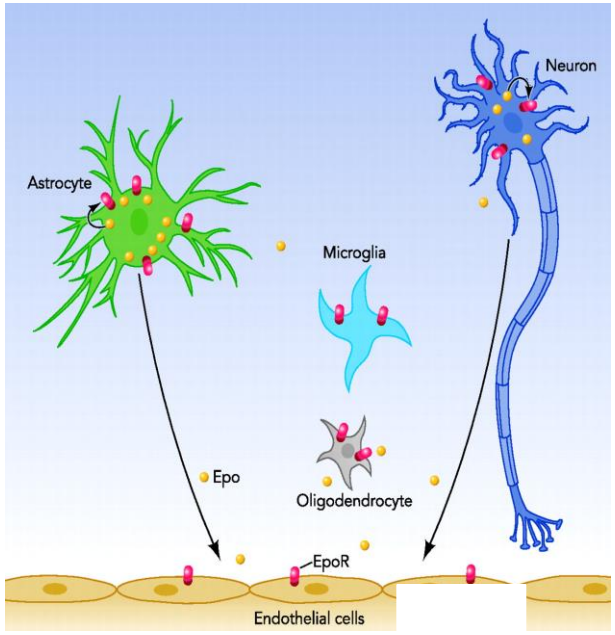
Neuroprotektion bei Frühgeborenen

- Mechanismen
- **Neuroprotektive Strategien**
  - **- *Erythropoietin (EPO)***
  - *- jenseits von EPO*

EPO und EPO Rezeptor – neuroprotektive Ziele







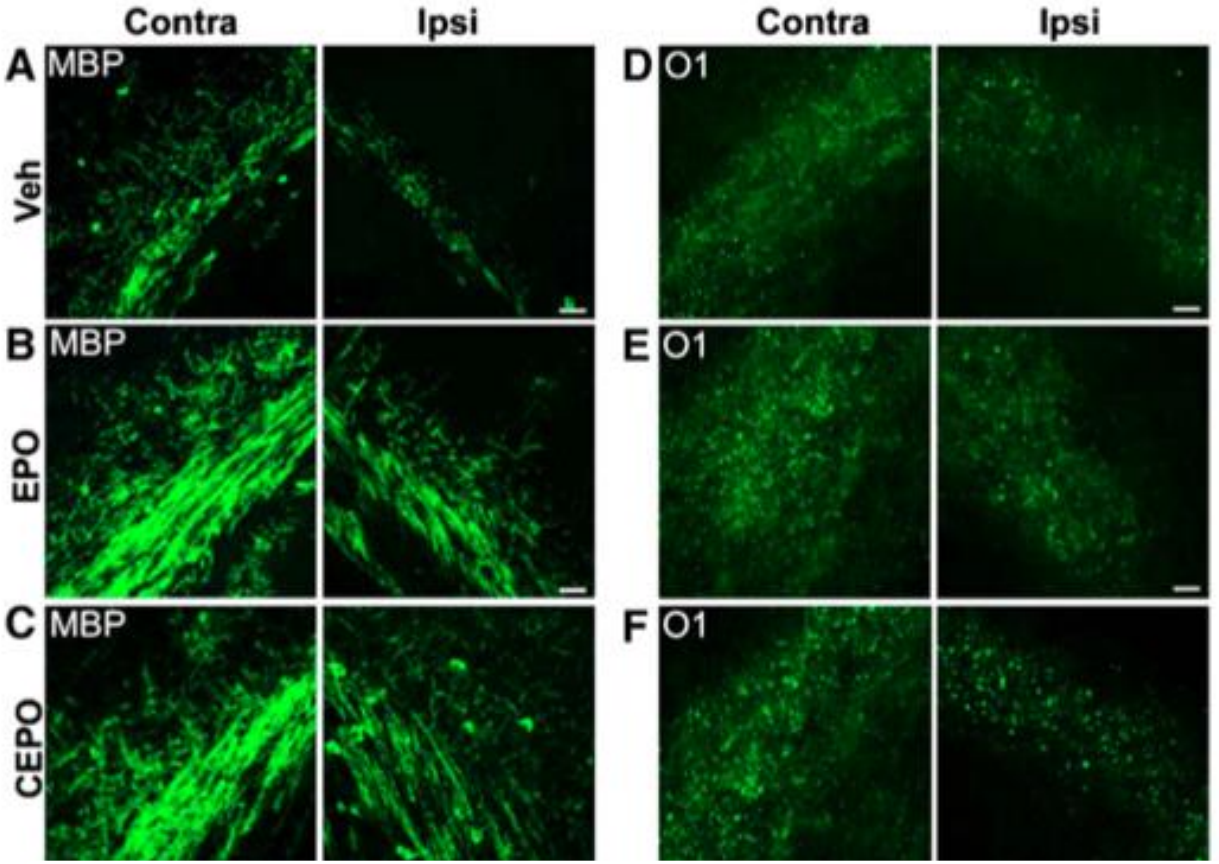
Juul et al. Clin Perinatol 2015, Ostrowski et al. J Clin Med. 2018

EPO schützt unreife Oligodendrozyten

Occlusion A. Carotis
O_2 6 %, 35 min

+/- LPS i.p.

+/- Epo/cEpo 5000IE



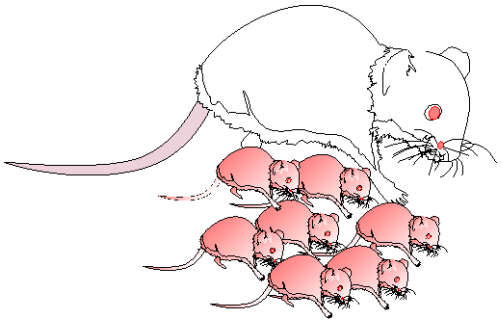
Liu et al. Exp Neurol. 2011

Sauerstofftoxizität – experimentelles Modell

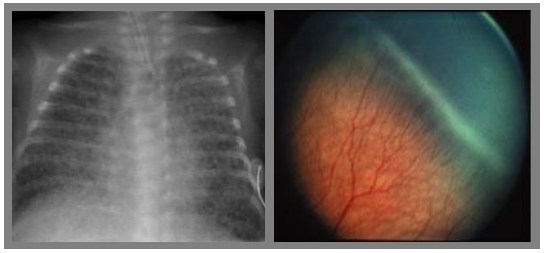
PaO_2: 75 mmHg

PaO_2: 25 mmHg

preterm birth



80%O_2



hyperoxia (80% O_2)
or
normoxia (21% O_2)
24-48 hrs

follow-up

Birth

p5

p6, 11,
21, 30, 60, 120

Felderhoff-Mueser et al. Neurobiol Dis 2004

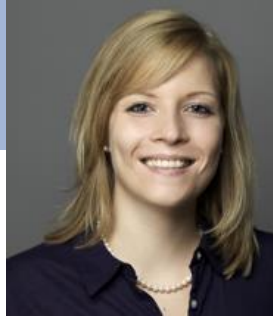
Gerstner et al. Ann Neurol 2008

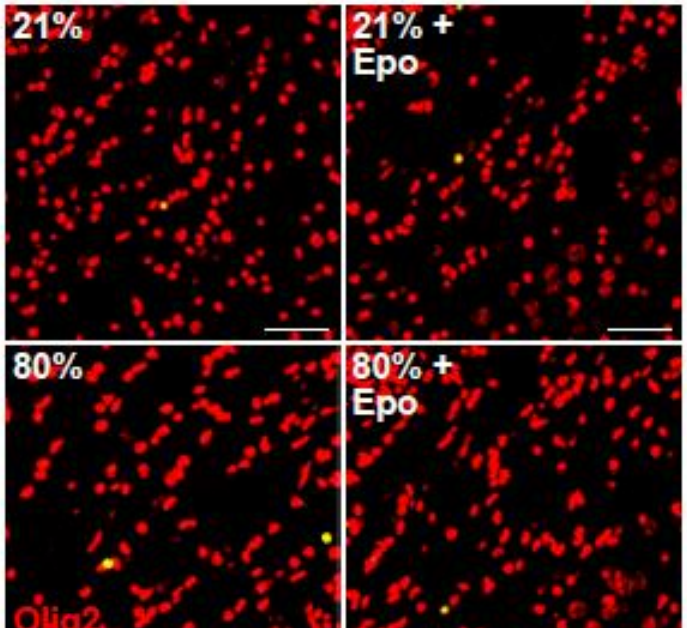
Dzietko et al. Ann Neurol 2009

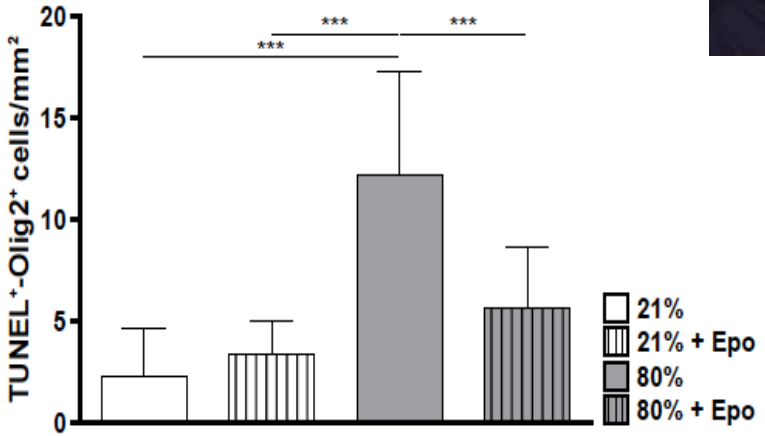
Sifringer et al. Cell Death Dis 2012

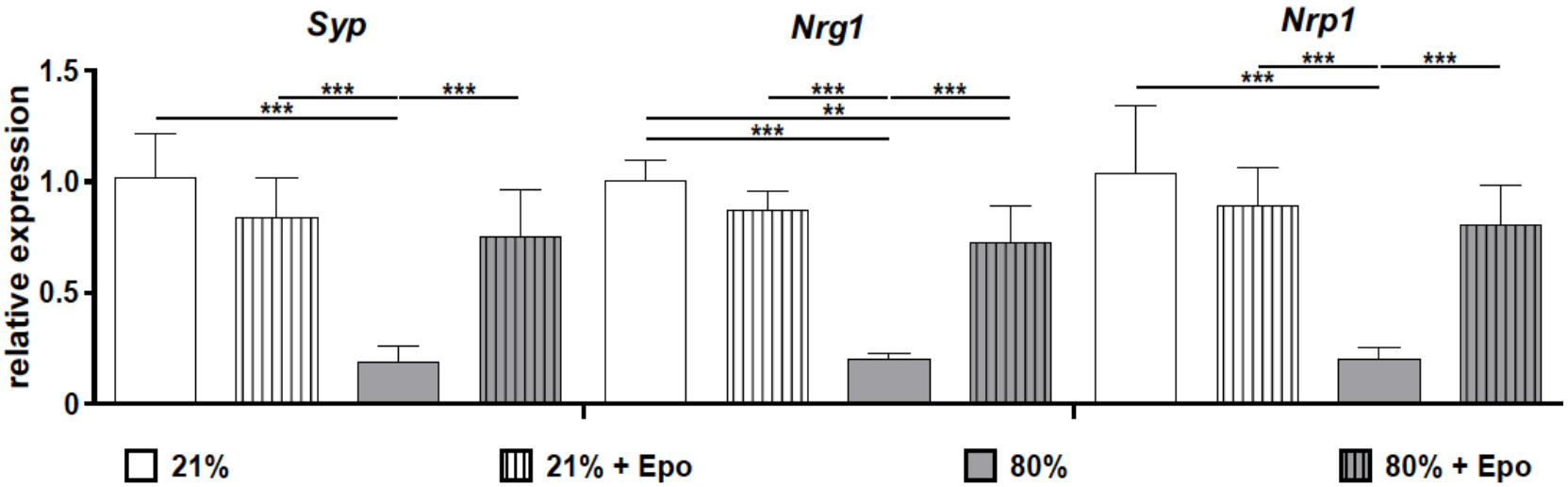
Collins MP (2001) ….. ventilation-related risk factors for cerebral palsy in low birth weight infants. Ped Res, 50:712-719

EPO reduziert die Hyperoxie-induzierte Hirnschädigung



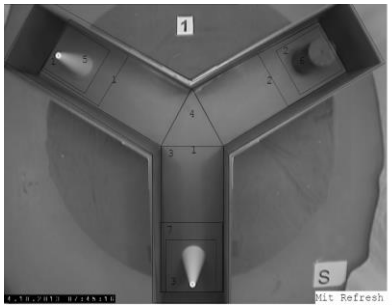


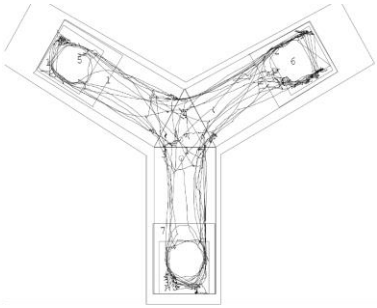


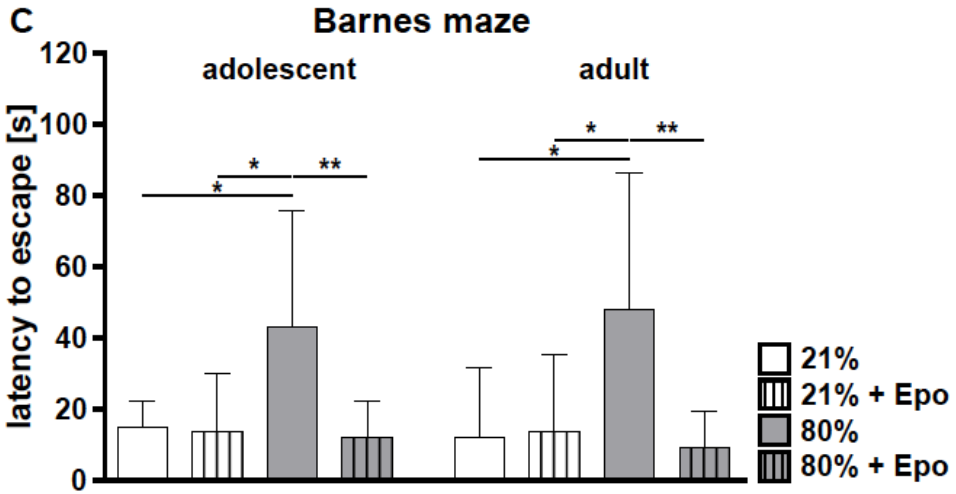


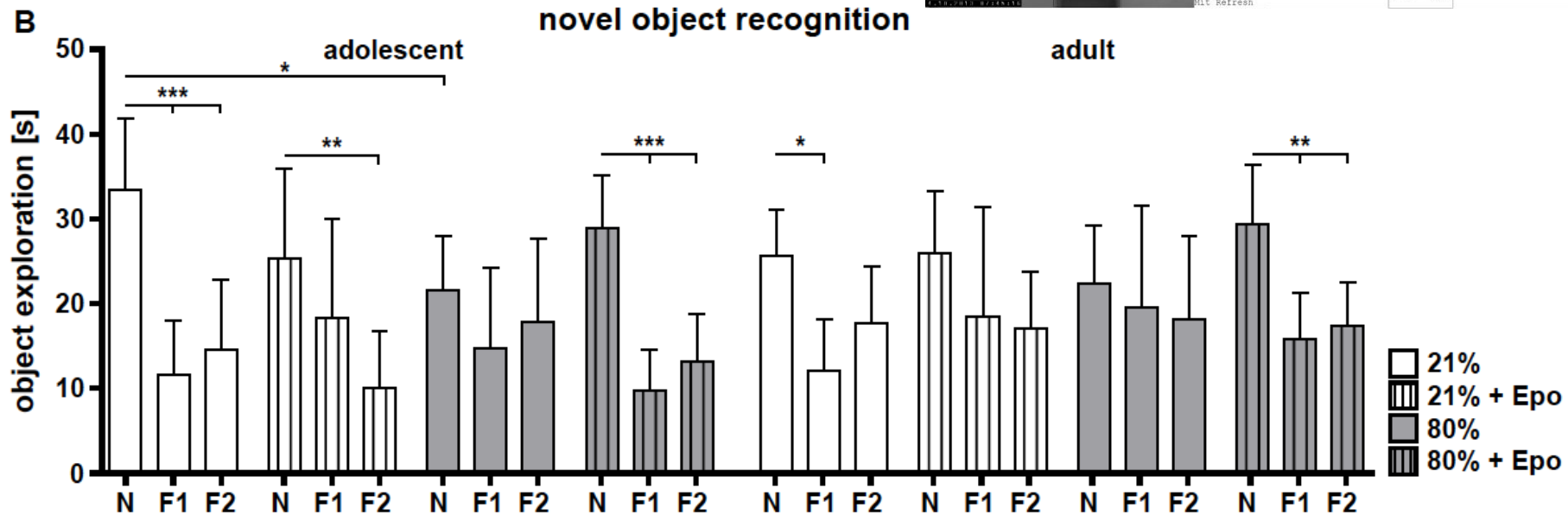
Sifringer et al. Int J Mol Sci 2012
Hoeber et al. 2016 Oxid Med Cell Longev 2016

Hyperoxie-induzierte Auswirkung auf die Kognition









Hoeber et al. 2016 Oxid Med Cell Longev

EPO – klinische Studien bei Frühgeborenen

Studies	Year	n	Inclusion criteria	rhEpo dose	Neurodevelopmental outcome			p
					criteria	rhEpo	placebo	
Newton	1999	40	≤1,250 g	500 or 1,000 U/kg/week	MDI at 17 months	95.4±9.9	94.6±18.7	NS
Ohls	2001	102	≤1,000 g	1,200 U/kg/week	% MDI <70 at 18–22 months	31%	36%	NS
					% PDI <70 at 18–22 months	31%	13%	<0.05
					% CP at 18–22 months	19%	18%	NS
Bierer	2006	12	≤1,000 g	1,200 U/kg/week	% MDI <70 at 18–22 months	96±11/78±7*		<0.05
Neubauer	2010	146	<1,000 g	750 or 1,500 U/kg/week	IQ score at 10–13 years	90.8±17.2	81.3±21.1	<0.005
					normal development	55%	39%	<0.05
McAdams	2013	35	<1,000 g	500, 1,000 or 2,500 U/kg (3 doses)	cognitive score from 4 to 36 months	Δ score = 5.3		0.044
					motor score from 4 to 36 months	Δ score = 7.5		0.026
Fauchère	ongoing	420	<32 weeks	3,000 U/kg (3 doses)	Keine Signifikanz mit 24 Monaten und 5 Jahren !			
Juul	ongoing	940	<28 weeks	1,000 U/kg (6 doses) and then 400 IU/kg/week until 33 weeks	MDI and PDI at 24–26 months	results expected in 2018		

Favrais et al. Neonatology 2014, Natalucci et al. YAMA 2016, jENS meeting 2019

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M. O'Shea,
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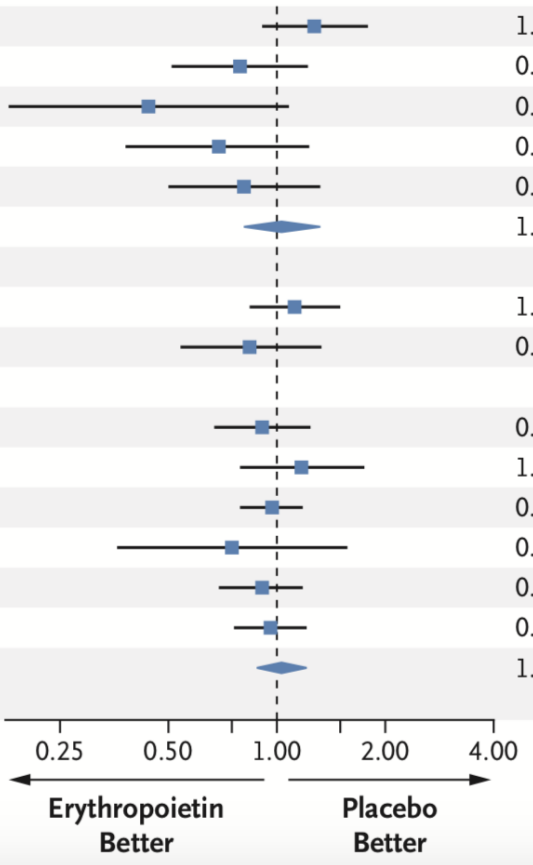
Table 1. Maternal, Pregnancy, and Infant Characteristics at Enrollment.*

Characteristic	Erythropoietin (N=476)	Placebo (N=460)
Maternal characteristics		
Age — yr	29.1±6.2	28.8±6.2
Hispanic ethnic group — no. (%)†	104 (22)	96 (21)
Race — no. (%)†		
White	309 (65)	302 (66)
Black	131 (28)	109 (24)
Unknown or not reported	36 (8)	49 (11)
Education — no. (%)		
High school or less	148 (31)	159 (35)
Some college	153 (32)	132 (29)
College degree or greater	113 (24)	119 (26)
Unknown or not reported	62 (13)	50 (11)
Pregnancy characteristics		
Complications of pregnancy		
Maternal indications for delivery — no. (%)‡	76 (16)	76 (17)
Risk of infection — no. (%)§	349 (73)	340 (74)
Pregnancy-induced hypertension — no. (%)	39 (8)	32 (7)
Prenatal glucocorticoid use — no. (%)	430 (90)	412 (90)
Prenatal magnesium sulfate use — no. (%)	374 (79)	375 (82)
Delivery complications — no. (%)¶	79 (17)	70 (15)
Cesarean delivery — no. (%)	337 (71)	314 (68)
Delayed cord clamping — no./total no. (%)	171/346 (49)	147/334 (44)
Pregnancy with multiple fetuses — no. (%)	125 (26)	118 (26)
Infant characteristics		
Female sex — no. (%)	219 (46)	229 (50)
Gestational age at birth — no. (%)		
24 wk	113 (24)	119 (26)
25 wk	121 (25)	124 (27)
26 wk	103 (22)	118 (26)
27 wk	139 (29)	99 (22)
Mean gestational age at birth — wk	26.0±1.2	25.8±1.1
Weight — g	806.4±194.6	792.9±182.2
Weight <10th percentile for gestational age — no. (%)	69 (14)	78 (17)
Head circumference <10th percentile — no. (%)	80 (17)	81 (18)
Apgar score at 5 min	6.1±2.2	6.2±2.1
Apgar score <5 at 5 min — no. (%)	104 (22)	85 (18)
Intracranial hemorrhage before first infusion — no. (%)	100 (21)	94 (20)
Median age at first infusion (interquartile range) — hr	21.1 (15.3–23.5)	20.0 (14.8–23.3)

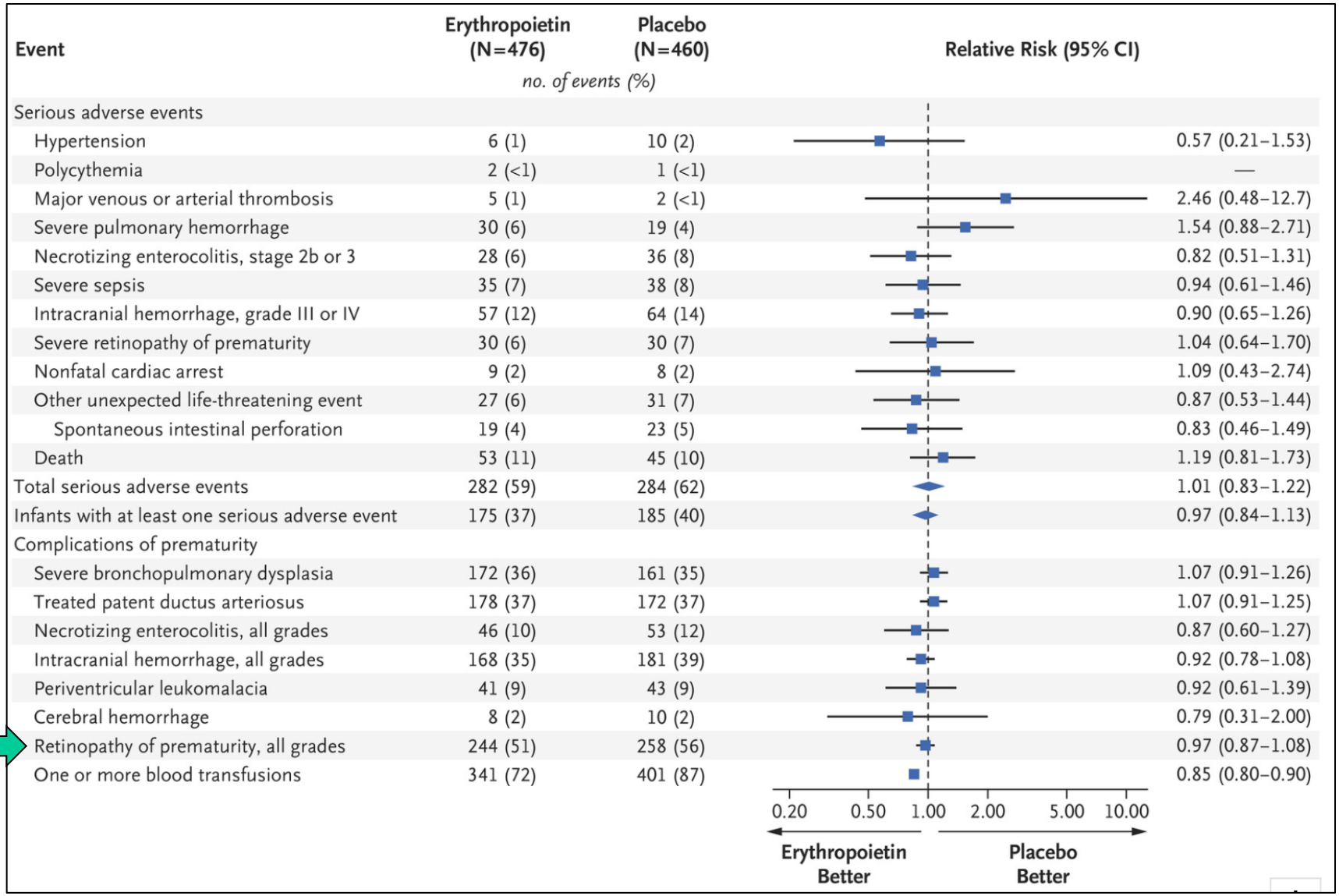
PENUT – EPO bringt keine signifikante Verbesserung des Outcome

Outcome	Erythropoietin	Placebo	Relative Risk (95% CI)
	no. of events/total no. (%)		
Death	63/476 (13)	50/460 (11)	1.27 (0.91–1.79)
Severe neurodevelopmental impairment	34/313 (11)	44/315 (14)	0.79 (0.51–1.22)
Severe cerebral palsy	8/313 (3)	18/315 (6)	0.44 (0.18–1.08)
Bayley-III composite cognitive score <70	19/311 (6)	28/314 (9)	0.69 (0.38–1.23)
Bayley-III composite motor score <70	28/310 (9)	36/314 (11)	0.81 (0.50–1.32)
Death or severe neurodevelopmental impairment	97/376 (26)	94/365 (26)	1.03 (0.81–1.32)
Gestational age at birth			
24 wk 0 days to 25 wk 6 days	67/190 (35)	62/197 (31)	1.12 (0.84–1.50)
26 wk 0 days to 27 wk 6 days	30/186 (16)	32/168 (19)	0.84 (0.54–1.33)
Sex			
Male	59/201 (29)	57/183 (31)	0.91 (0.67–1.24)
Female	38/175 (22)	37/182 (20)	1.17 (0.79–1.75)
Moderate-to-severe neurodevelopmental impairment	118/312 (38)	120/314 (38)	0.97 (0.79–1.18)
Moderate-to-severe cerebral palsy	13/311 (4)	18/315 (6)	0.75 (0.36–1.57)
Bayley-III composite cognitive score <85	77/311 (25)	87/314 (28)	0.91 (0.69–1.18)
Bayley-III composite motor score <85	95/310 (31)	96/314 (31)	0.96 (0.76–1.21)
Death or moderate-to-severe neurodevelopmental impairment	181/375 (48)	170/365 (47)	1.03 (0.88–1.21)



Juul et al. N Engl J Med 2020

PENUT – EPO hat keine signifikanten Nebenwirkungen



Event	Erythropoietin (N=476)	Placebo (N=460)	Relative Risk (95% CI)
	no. of events (%)		
Serious adverse events			
Hypertension	6 (1)	10 (2)	0.57 (0.21–1.53)
Polycythemia	2 (<1)	1 (<1)	—
Major venous or arterial thrombosis	5 (1)	2 (<1)	2.46 (0.48–12.7)
Severe pulmonary hemorrhage	30 (6)	19 (4)	1.54 (0.88–2.71)
Necrotizing enterocolitis, stage 2b or 3	28 (6)	36 (8)	0.82 (0.51–1.31)
Severe sepsis	35 (7)	38 (8)	0.94 (0.61–1.46)
Intracranial hemorrhage, grade III or IV	57 (12)	64 (14)	0.90 (0.65–1.26)
Severe retinopathy of prematurity	30 (6)	30 (7)	1.04 (0.64–1.70)
Nonfatal cardiac arrest	9 (2)	8 (2)	1.09 (0.43–2.74)
Other unexpected life-threatening event	27 (6)	31 (7)	0.87 (0.53–1.44)
Spontaneous intestinal perforation	19 (4)	23 (5)	0.83 (0.46–1.49)
Death	53 (11)	45 (10)	1.19 (0.81–1.73)
Total serious adverse events	282 (59)	284 (62)	1.01 (0.83–1.22)
Infants with at least one serious adverse event	175 (37)	185 (40)	0.97 (0.84–1.13)
Complications of prematurity			
Severe bronchopulmonary dysplasia	172 (36)	161 (35)	1.07 (0.91–1.26)
Treated patent ductus arteriosus	178 (37)	172 (37)	1.07 (0.91–1.25)
Necrotizing enterocolitis, all grades	46 (10)	53 (12)	0.87 (0.60–1.27)
Intracranial hemorrhage, all grades	168 (35)	181 (39)	0.92 (0.78–1.08)
Periventricular leukomalacia	41 (9)	43 (9)	0.92 (0.61–1.39)
Cerebral hemorrhage	8 (2)	10 (2)	0.79 (0.31–2.00)
Retinopathy of prematurity, all grades	244 (51)	258 (56)	0.97 (0.87–1.08)
One or more blood transfusions	341 (72)	401 (87)	0.85 (0.80–0.90)

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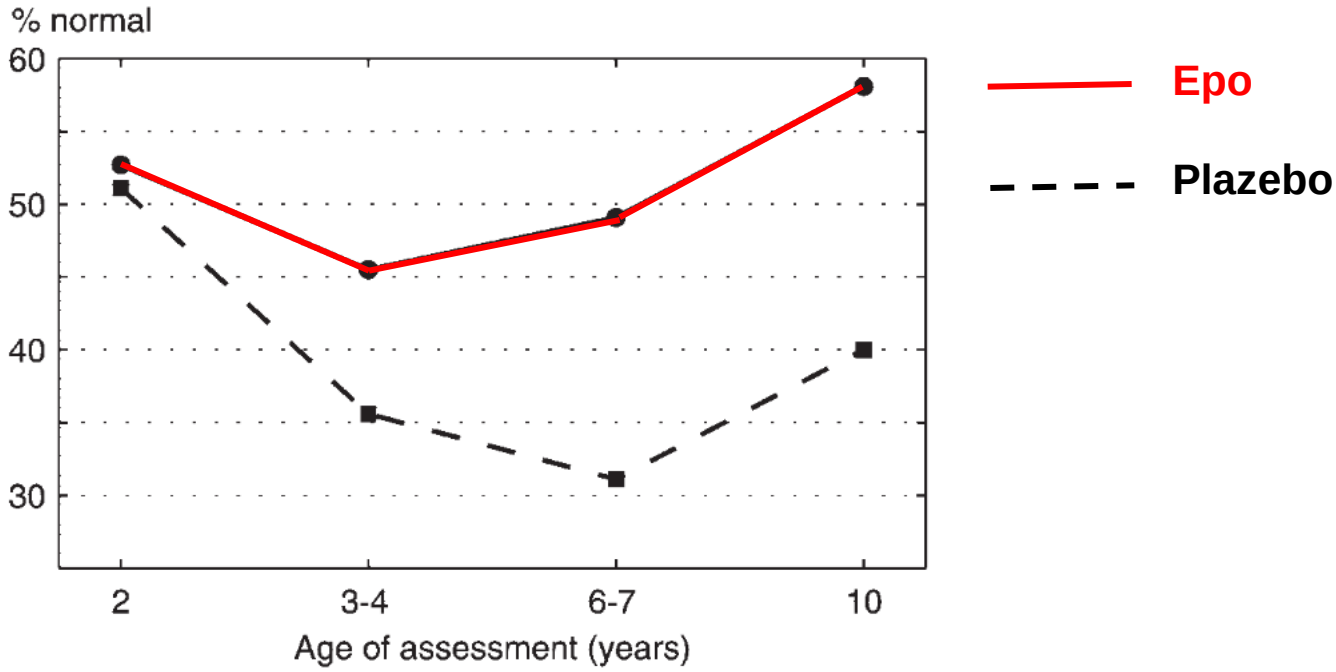
Auswirkungen von EPO auf die Langzeitentwicklung (retrospektiv !)



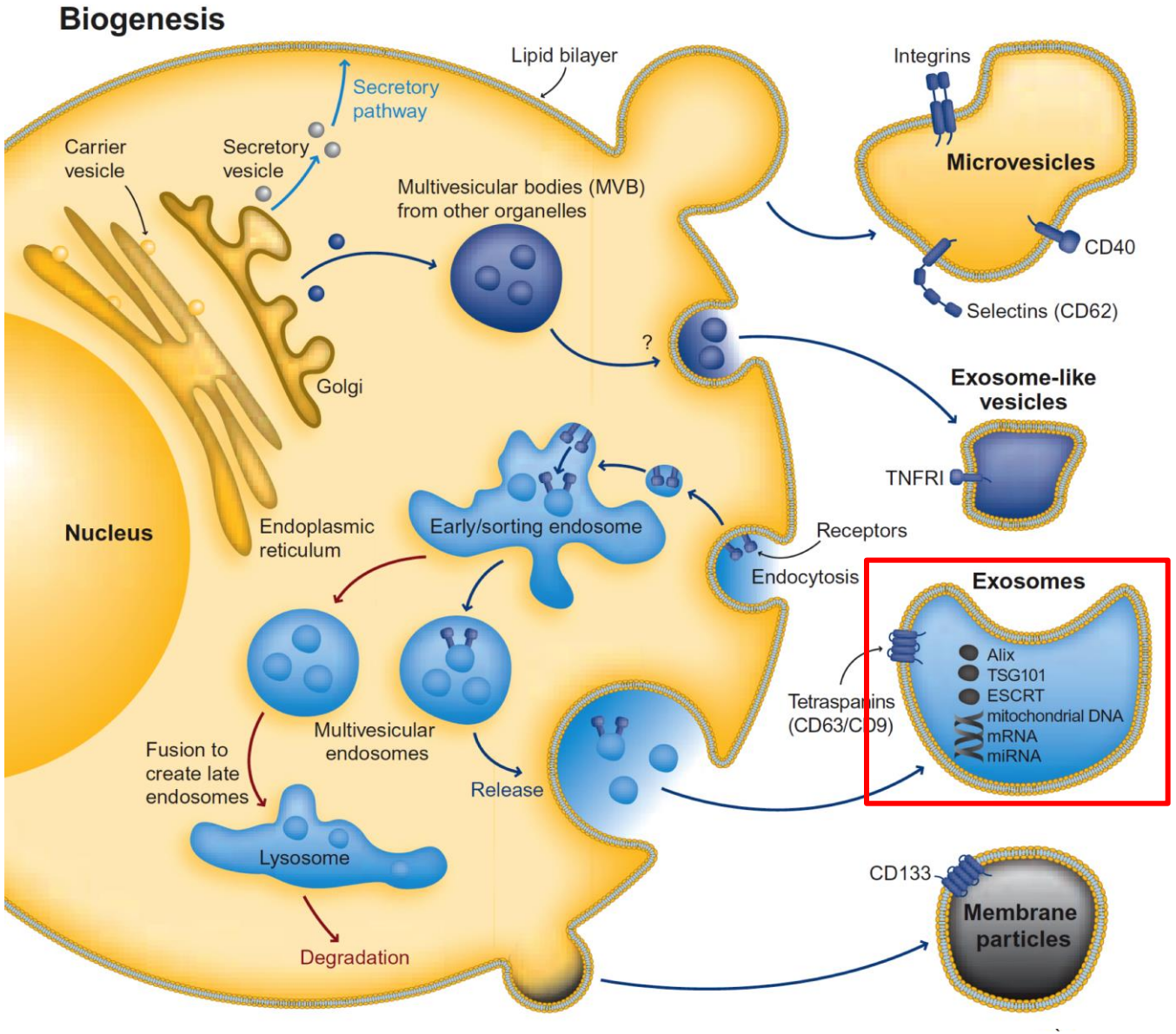
Neubauer et al. Ann Neurol 2010

Neuroprotektion bei Frühgeborenen

- Mechanismen
- **Neuroprotektive Strategien**
  - *Erythropoietin (EPO)*
  - ***jenseits von EPO: Stammzellen***

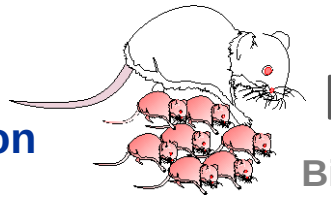
Mesenchymale Stammzellen und Exosomen (MSC-EV)

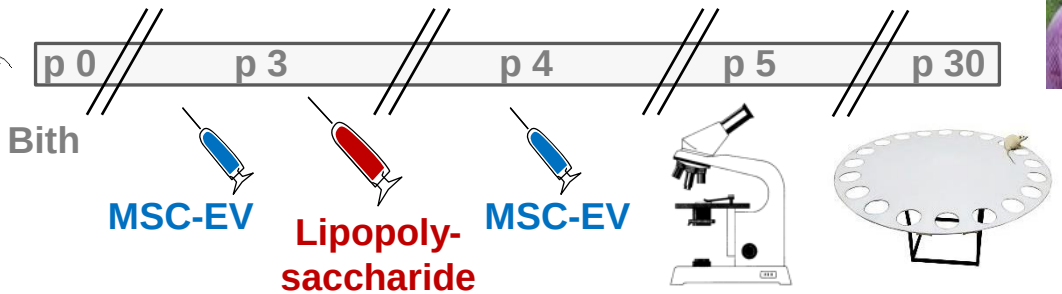
- immunmodulatorisch
- Regenerativ
- aus der Nabelschnur !



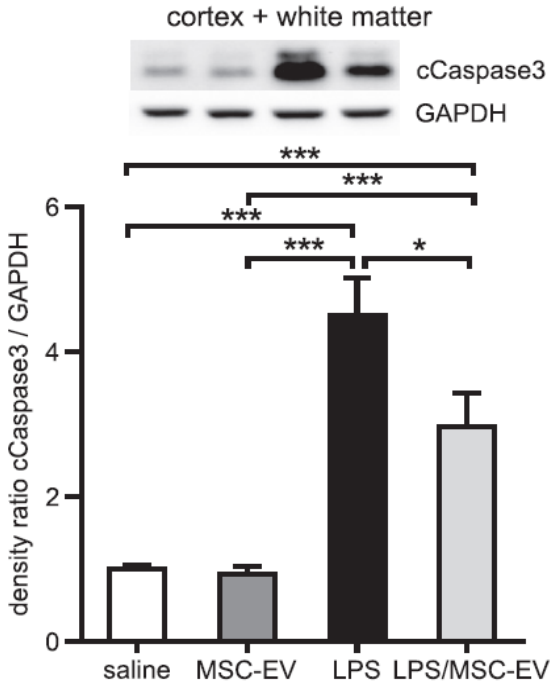
Exosomen zur Behandlung der Hirnschädigung des FG

Perinatal inflammation

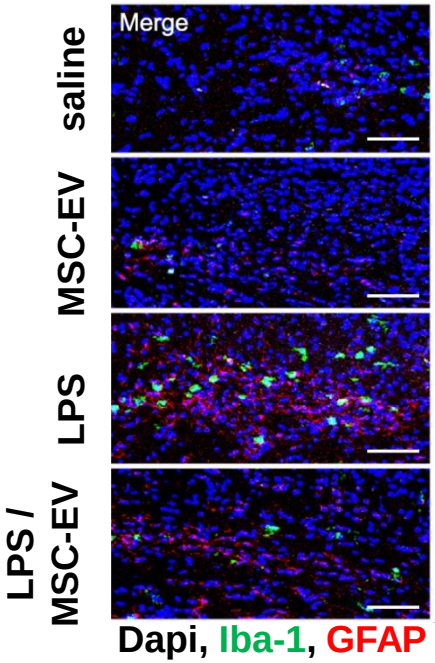




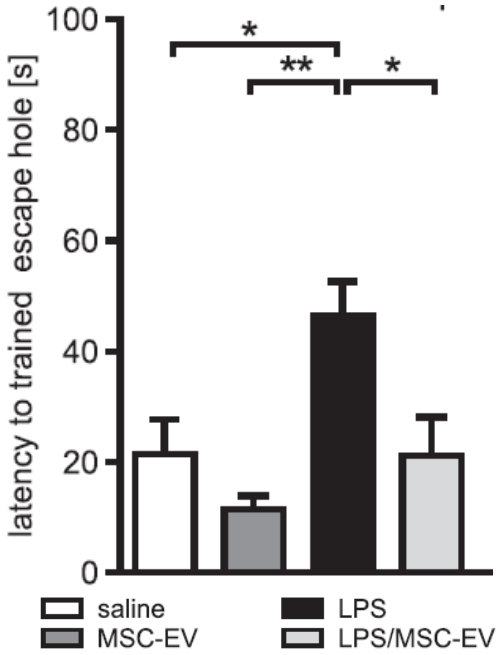
cellular degeneration



astro- and microgliosis



cognitive function (Barnes maze)

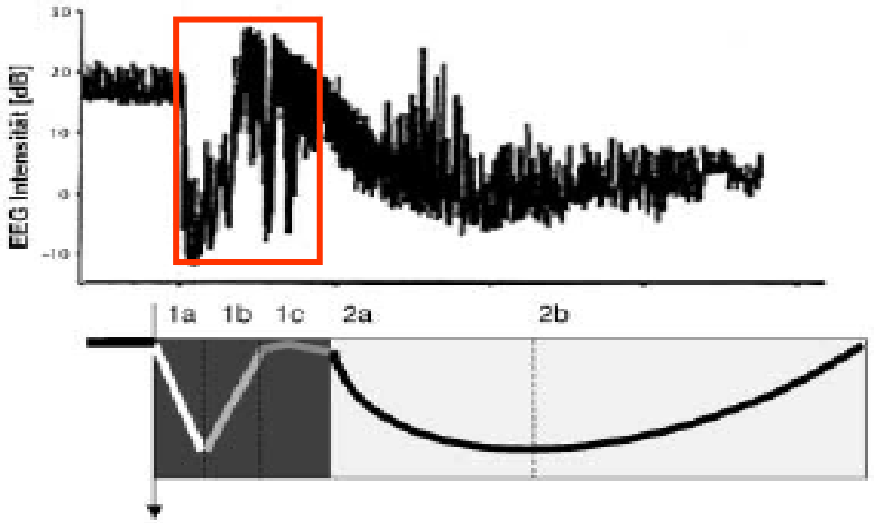


Drommelschmidt et al. (2017) Brain Behav Immun.

Neuroprotektion bei Reifgeborenen

- **Mechanismen**
- Neuroprotective strategies
  - *Erythropoietin (EPO)*
  - *cell based regenerative therapies*

Zielmechanismen zur Neuroprotektion



therapeutic window

tertiary phase

- *Stem cells*
- *EPO*
- *extracellular vesicles*

primary

- *Allopurinol*
- *EPO*
- *Xenon*
- *Melatonin*

secondary energy failure

- *EPO*
- *Xenon*
- *anti-apoptotic drugs*
- *Melatonin*

For review: Felderhoff-Müser U. Ped Adolesc Med 2020

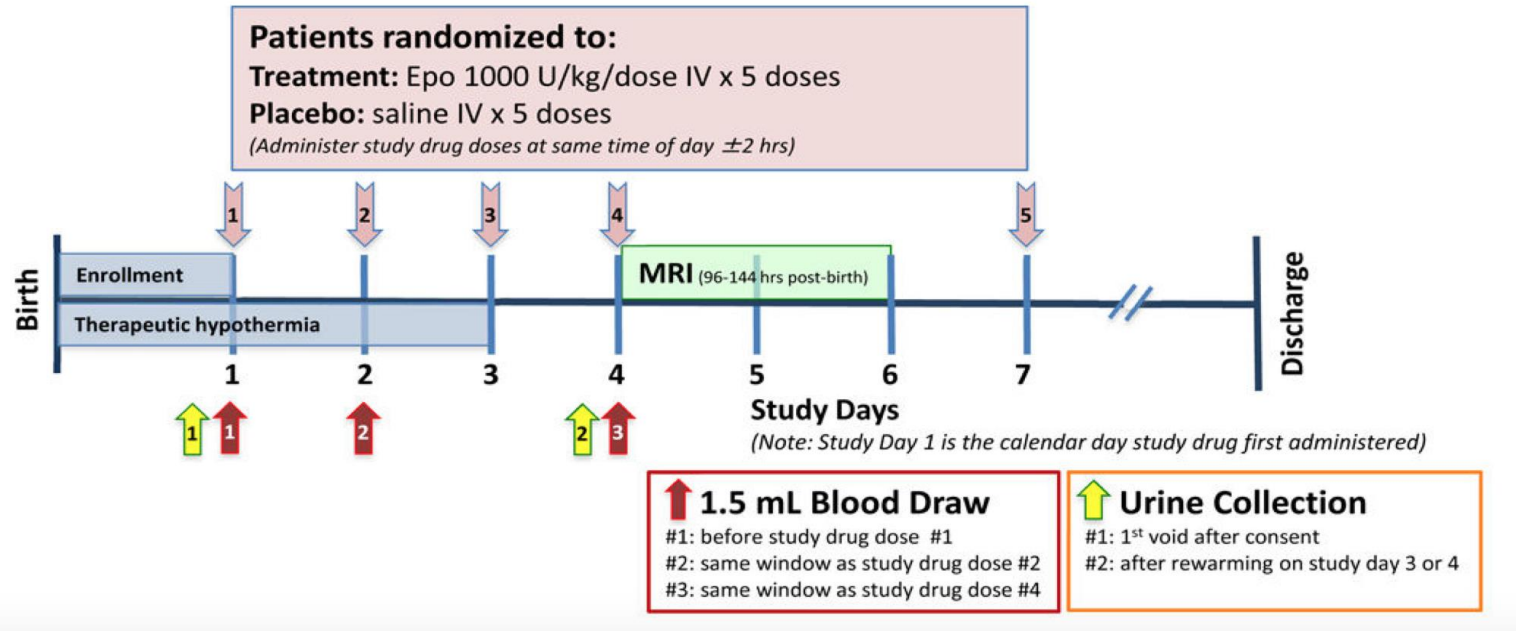
Hypothermie zur Behandlung der Asphyxie

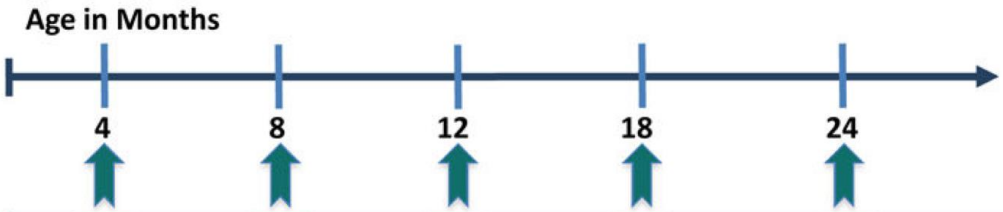
"Cooling of the asphyxiated newborn infant is both safe and beneficial" –
NNT = 7 - 8

- 11 randomised controlled study (1505 infants)
- term born, >35 SSW
- reduction of mortality and morbidity at 18 months
  (RR 0,75 (95% CI 0,68-0,83); RD (-0,15, CI -0,2-0,1)), **NNT 7**
- mortality (RR 0,75 (95% CI 0,64-0,88; RD -0,09 (95% CI 0,13-0,04)),
  NNT 11, 11 trials
- neurolog. morbidity (RR 0,77 (95% CI 0,63 – 0,94); RD -0,13 (95% CI 0,19-0,07))
  NNT 8, 8 trials

Cochrane Database Syst Rev 2013

Hochdosis Epo nach Asphyxie – HEAL study





Phone Follow-Up (4, 8, 12, 18, & 24 months)
Interval medical and social history
WIDEA (12, 18, & 24 months)

In-Clinic Follow-Up (24 months)
Bayley III
Standardized neurologic exam
Gross Motor Function Classification System (GMFCS)
Child Behavior Checklist (CBCL)

Juul et al. Neonatology 2018

Experimentelles Modell – Application von MSCs zur Regeneration

C57Bl/6

p 0 | p 9 | p 9 | p 12 | p 16 | p 30-51

birth

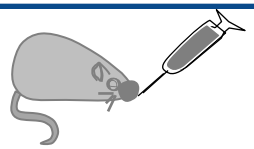
4 h
hypothermia /
normothermia

dpi 0 | dpi 3 | dpi 7 | dpi 21-42

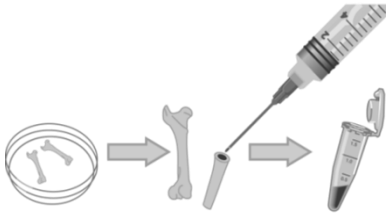
HIE

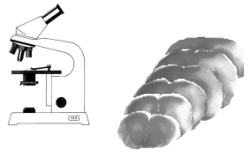
Occlusion of
A. *carotis communis*

60 min Hypoxie (10% O_2)
T_{rectal}=$T_{physiol.}$ = 35° C

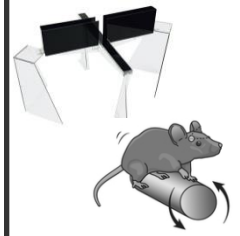


1x 10^6 intranasal MSC





Inflammation



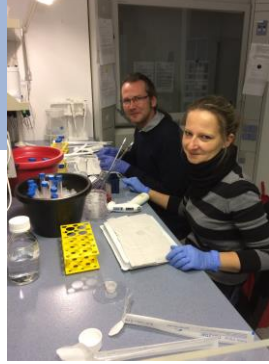
Function

experimental groups:

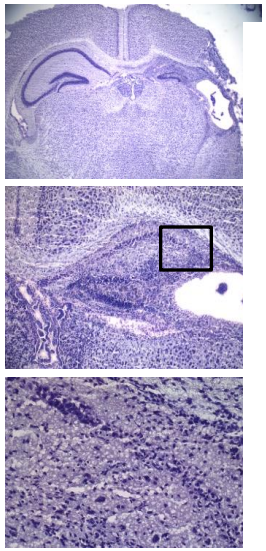
- Sham
- HI + normothermia (NT)
- HI + hypothermia (HT)
- HI + normothermia + MSC (MSC)
- HI + hypothermia + MSC (HT+MSC)

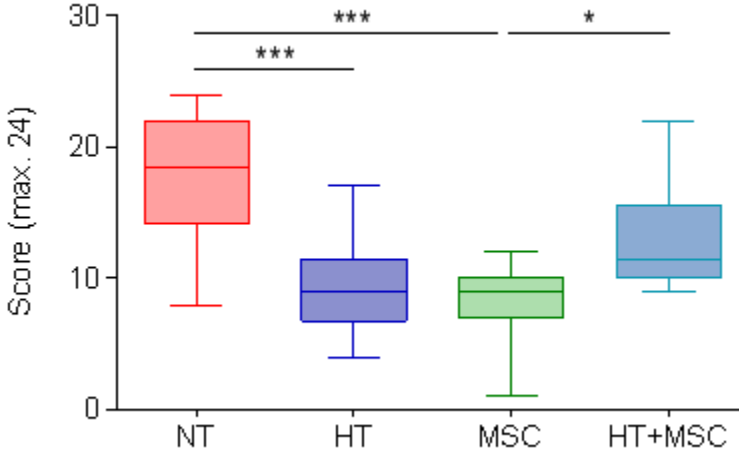
Herz et al. Exp Neurol 2016

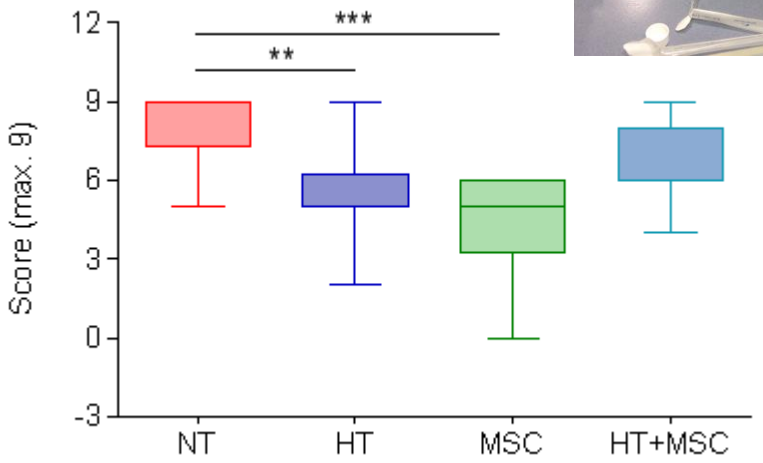
Morphologie - ☹☹☹



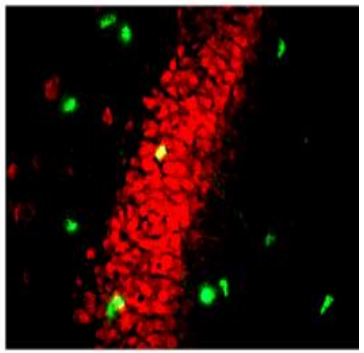
Injury Score – Tag 7



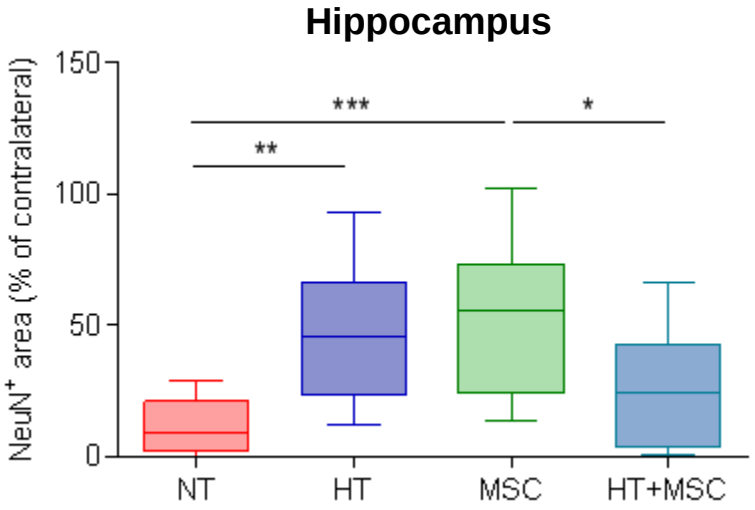




Neuronal density – Tag 7



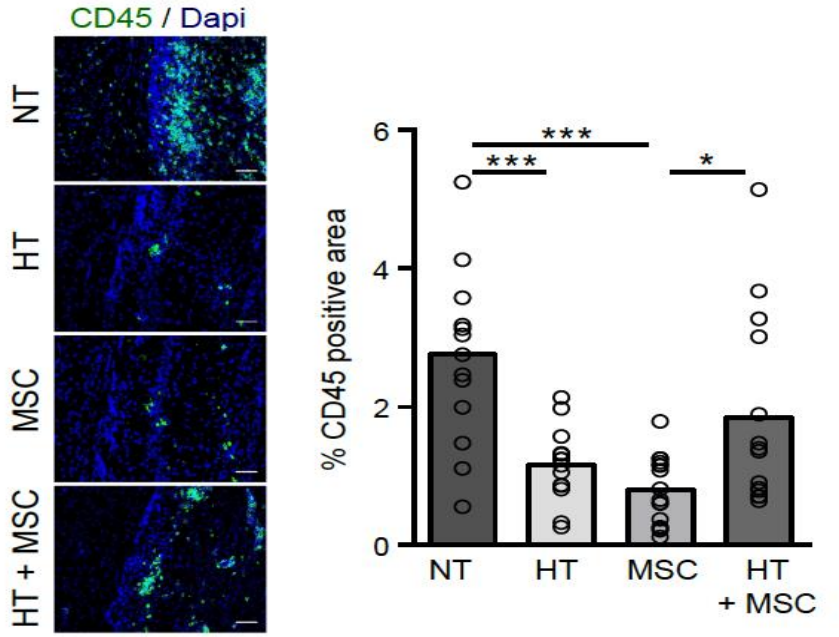
NeuN /Olig2

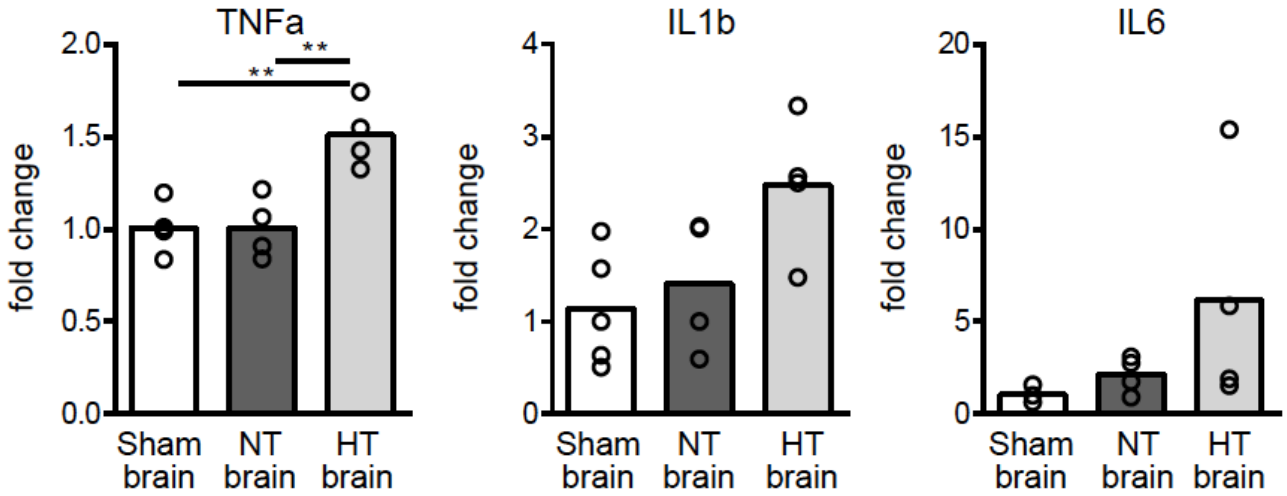


n=14-16/group

Herz et al. Brain Behav Immun 2018

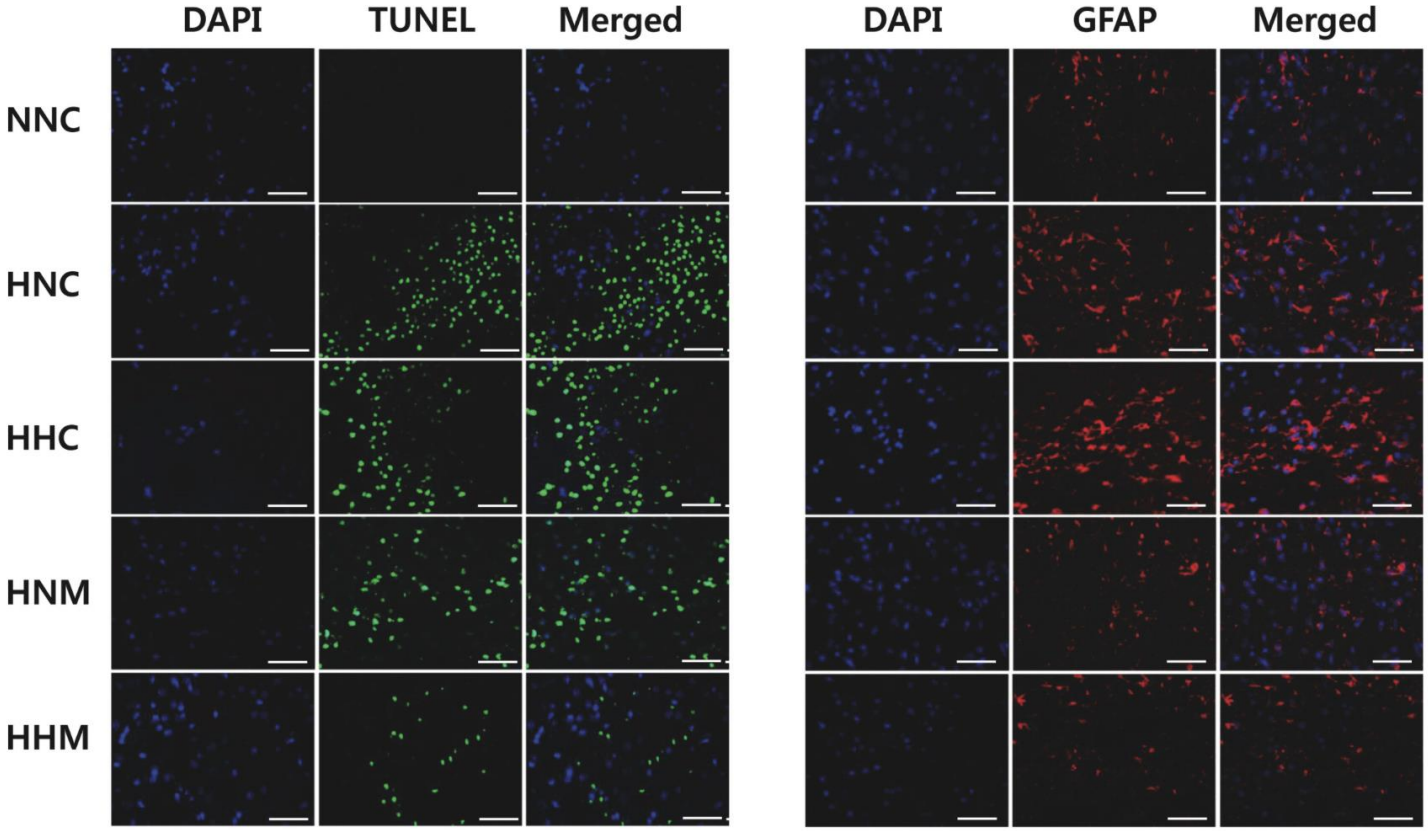
Hypothermie moduliert den Phänotyp von MSCs

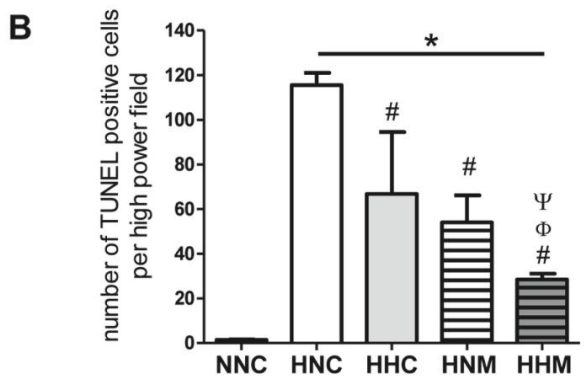


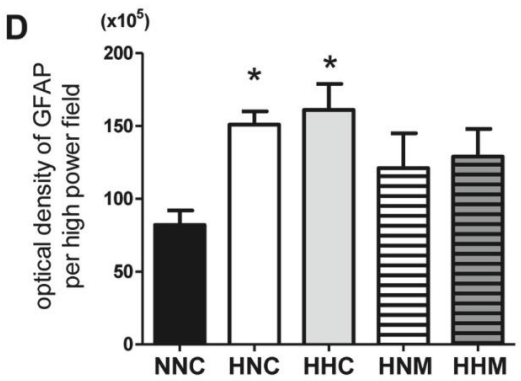


Herz et al. Brain Behav Immun 2018

MSCs und Hypothermie zur Behandlung der Asphyxie







Park et al. Plos one 2015, 2018

Mind the gap.....es gibt viel zu tun !

- Untersuchungen zu den Grundlagen der perinatalen Hirnschädigung

  - personalisierte Medizin ?

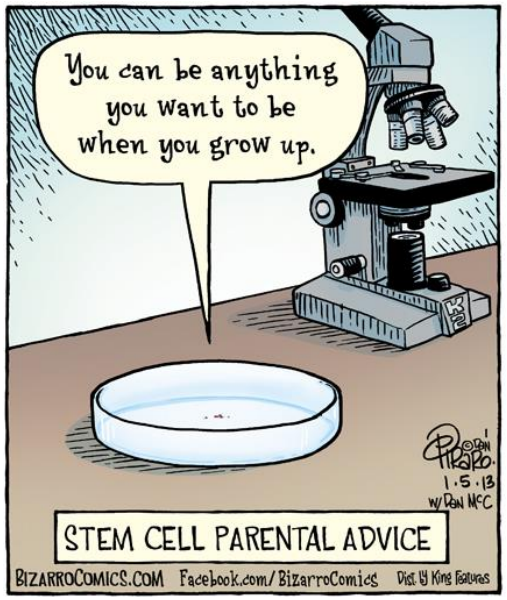
- Untersuchungen unterschiedlicher Stammzellpopulationen

- Entwicklung von off-the shelf MSC etc. Produkten

- Klinische Studien !

PREMSTEM

HORIZON 2020



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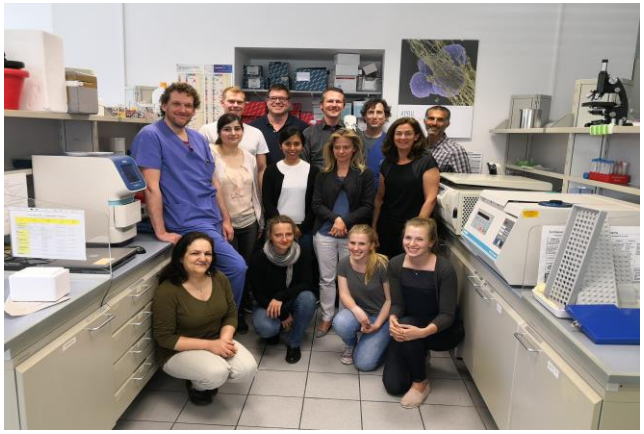
Meray Serdar



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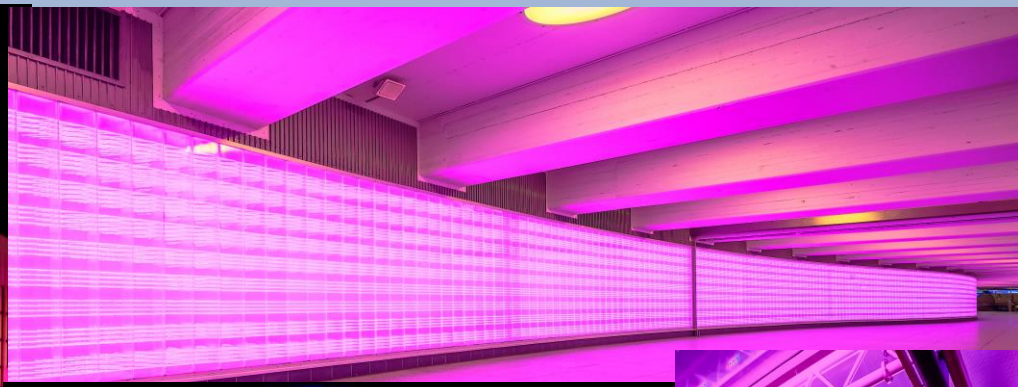
neobrain

PREMSTEM

DFG, EU FP6, HORIZON 2020, BMBF
Mercator Stiftung,
Sparkassenstiftung
Sonnenfeld Stiftung
CD Stiftung, Frenzen Stiftung
Kulturstiftung Essen
Stiftung Universitätsmedizin Essen
IFORES Programm
CHIESI, UCB, BioIncept

World Prematurity Day in Essen 17.11.2020 !



Purple for preemies

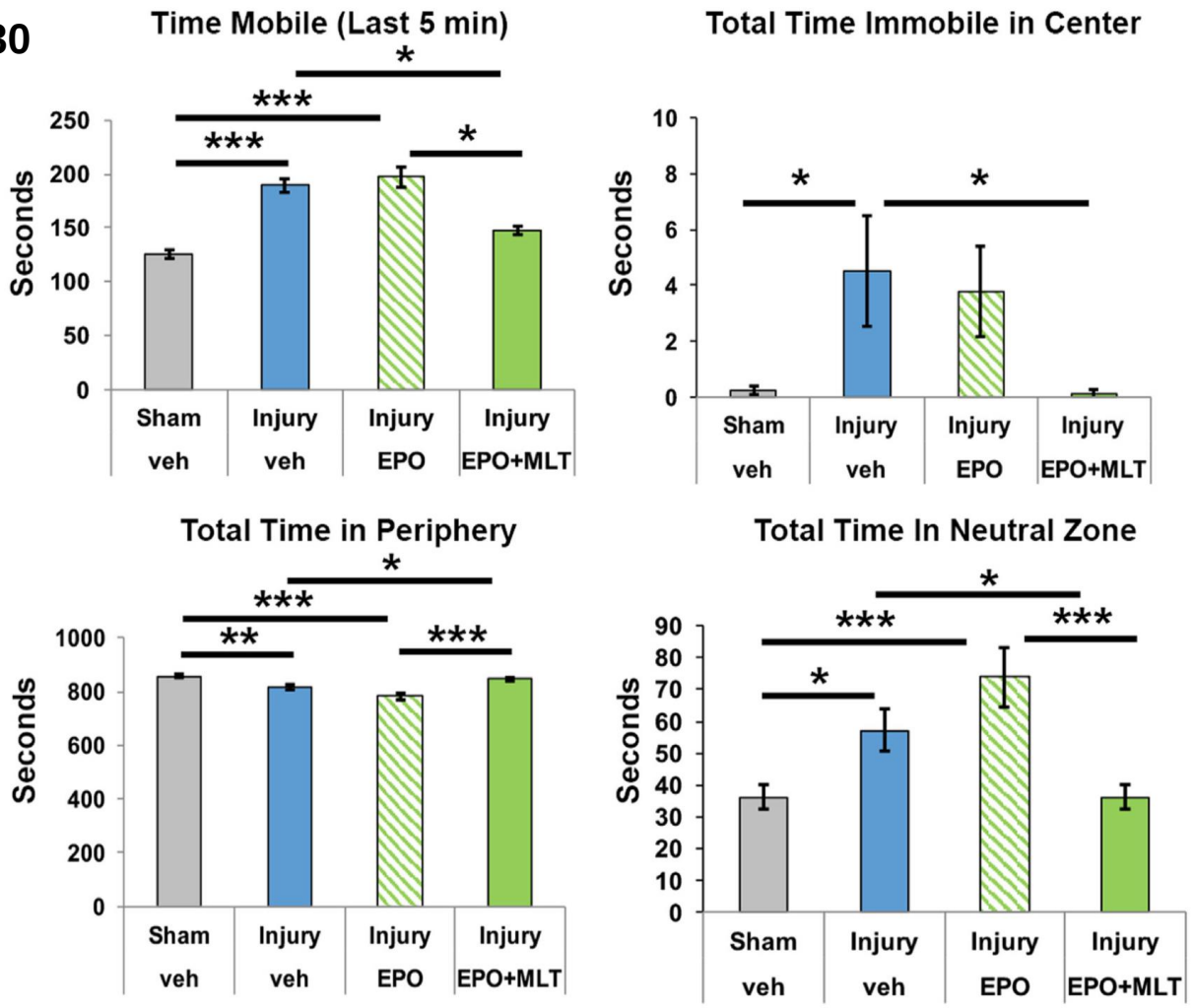
Vielen Dank !

Neuroprotektive Strategien im unreifen Gehirn

Risk	Therapy	Pre-clinical	Clinical (brain lesions)	Long term effects
Inflammation	• Antibiotics (Minocyclin) • NSAIDs (Indomethacin) • Antenatal steroids • **Immunmodulation**	+ + ++ +	0 + ++ 0	0 0 +/- 0
Hemodynamics	• Surfactant • Coffein • iNO • Inotropika	0 ++ + 0	++ (IVH) + +/- 0	+ + 0 0
Stress/pain	• Opiats	+/-	+/-	0
Growth factors/inflammation	• **Erythropoietin (Epo)** • **Stem cells**	+++ ++	+ 0	0 0
Excitoxicity/ free radikals	• Mg-Sulfat • Melatonin	+++ ++	+ -	-/+ -

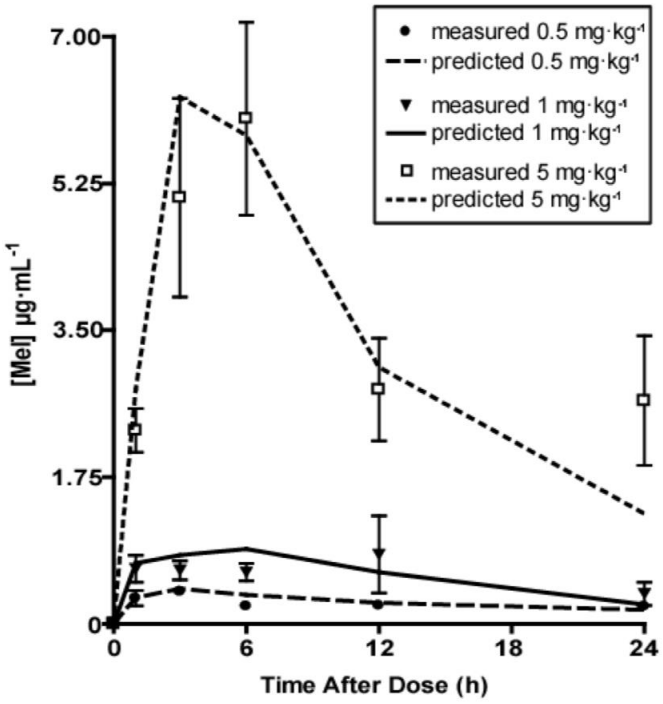
Placental insufficiency & Chorioamnionitis – Epo/MLT treatment

P30

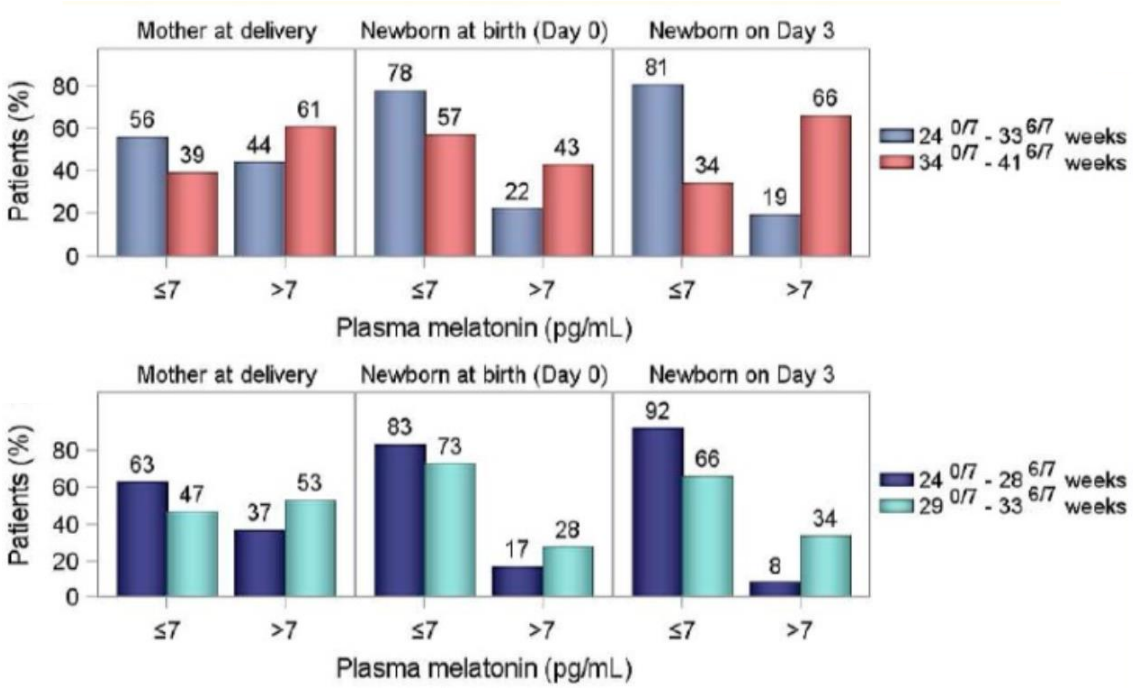


Jantzie et al. 2019 Front Neurol

Melatonin – plasma concentrations in preterm infants



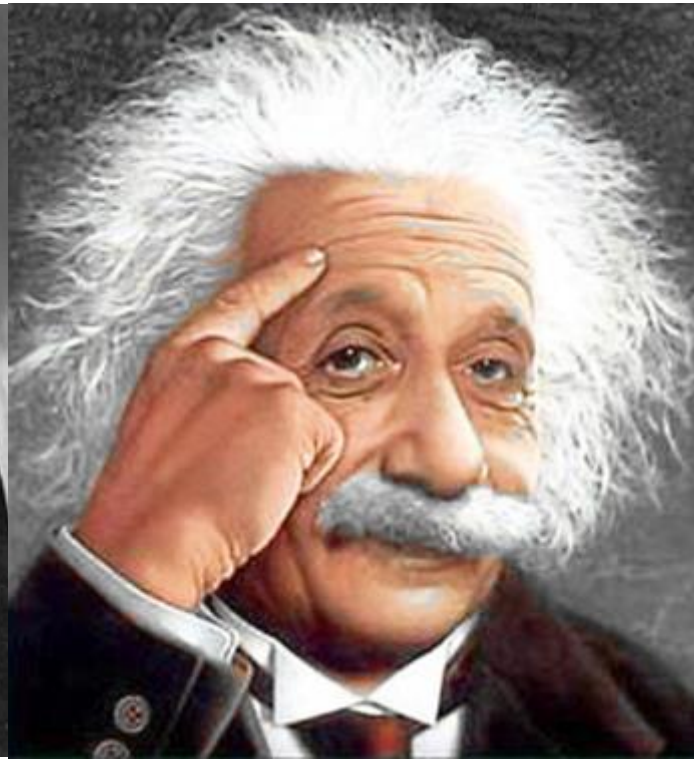
Carloni et al. Molecules 2017



Biran et al. Int J Mol Sci 2019 MELIP study

Sir Isaac Newton

Winston Churchill



Albert Einstein