UKD Universitätsklinikum Düsseldorf

José Carreras Stammzellbank
Düsseldorf Germany

HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

Biologische Vorteile von Nabelschnurblut für die regenerative Therapien
Unverwandte und gerichtete Nabelschnurblutspende - klinische Indikationen

Gesine Kögler

Institut für Transplantationsdiagnostik und Zelltherapeutika

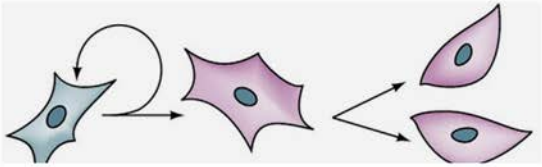
Düsseldorf

Pränatal- und Sterilitätsmedizin, Marl 18.10.2017

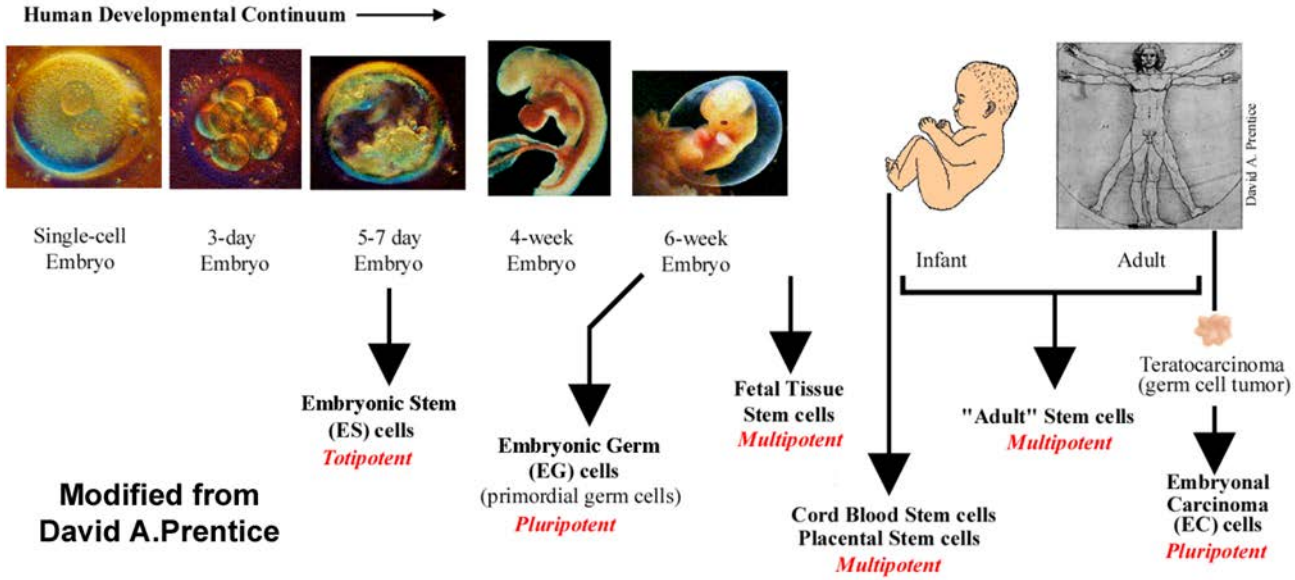
Themenschwerpunkte des Vortrages:

- Entwicklungspotential von Stammzellen während der fetalen Entwicklung
- Blutbildende Stammzellen im Nabelschnurblut und klinische Indikationen
- Unterschiede zwischen autologer und allogener verwandter und unverwandter Transplantation
- Angeborene/genetische Erkrankungen bei Kindern - worauf muss ich als Gynäkologe innerhalb der Familien achten
- Stromale Zellpopulationen im Nabelschnurblut zur Geweberegeneration
- Phase 1-3 Studien zu Ansätzen zur Behandlung des Diabetischen Fußes Neurale Regeneration (zerebrale Hirnschäden, Autismus, Schlaganfall) und mögliche Mechanismen
- Generierung von humanen induzierten pluripotenten Stammzellen aus Nabelschnurblut

Regenerative Medizin: Die Herkunft einer Stammzelle entscheidet über ihr Potential

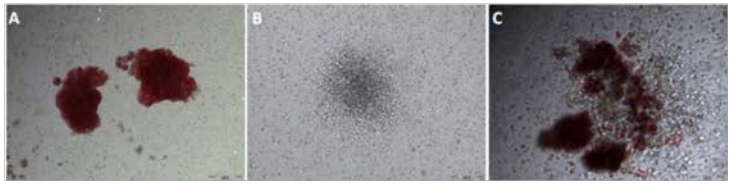


Stem Cells



Nabelschnurblut-blutbildende Stammzellen

Broxmeyer HE, et al: *Human umbilical cord blood as a potential source of transplantable hematopoietic stem/progenitor cells.* ***1985-1988***

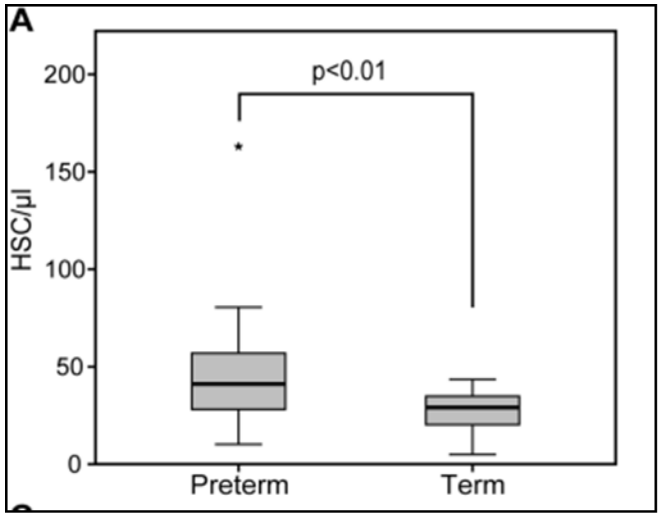


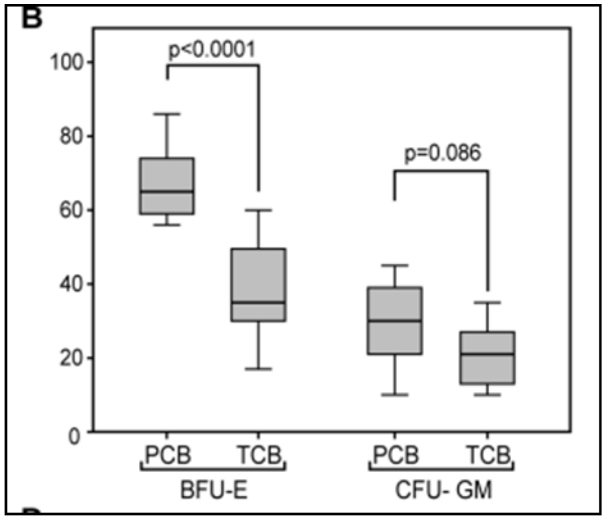
"We don't know why," says Broxmeyer!

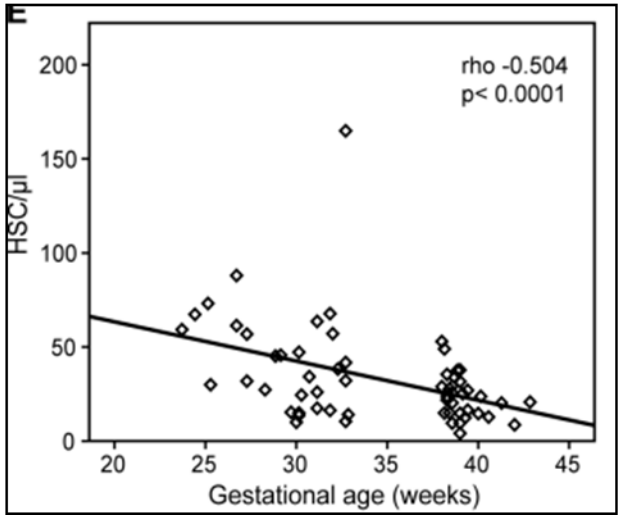
"It could be that the stem cells go back into the bone marrow. We don't know why there are so many stem cells at birth, and we don't know where they go."

The Art and Science of Medicine; Volume XXVI Number 1; Fall 2003

Qualität und Quantität hämatopoietischer Stammzellen







Preterm: 24-32 weeks

Term: 38-42 weeks

Wisgrill, L. et al. 2014

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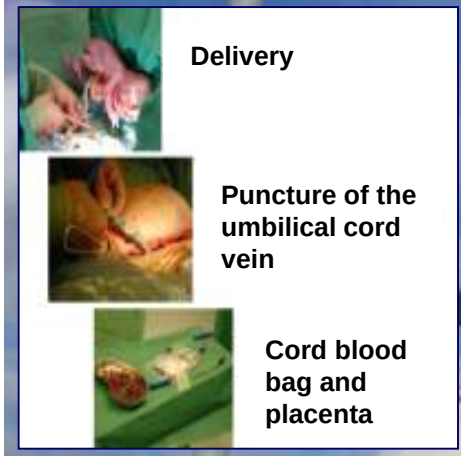
José Carreras Nabelschnurblutstammzellbank



Delivery

Puncture of the umbilical cord vein

Cord blood bag and placenta

Quality control

>26.000 kryokonservierte CBT
>1300 Nabelschnurbluttransplantate Düsseldorf transplantiert

60%Erwachsene Patienten

Automatic volume reduction using the SEPAX

Addition of cryoprotectant

Cryo-preservation in freezing cartridge

Automatic freezer

Storage at –196° C in liquid nitrogen

Shipment

Inventar José Carreras Stammzellbank Düsseldorf

Etabliert: 1992/1993

57 Kliniken (Januar 2017)

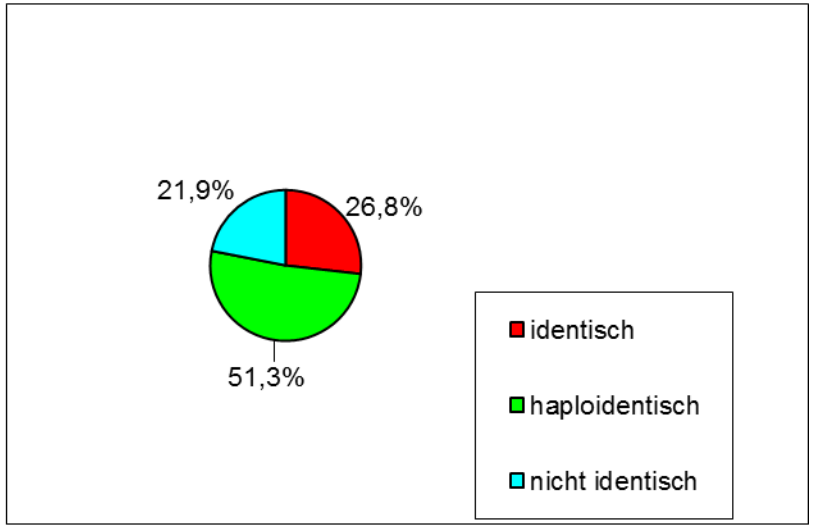
- **Art der Nabelschnurblutspenden (CB= cord blood)**
- **Ungerichtet unverwandt allogen**
- **Gerichtete allogene (Familie bei Indikation)**
- **allogene Spenden einschließlich Familienspenden N= 26775 (8/2017))**
  447 reservierte Familienspenden bei Indikation

Transplante:

N= 1310 (08/17)

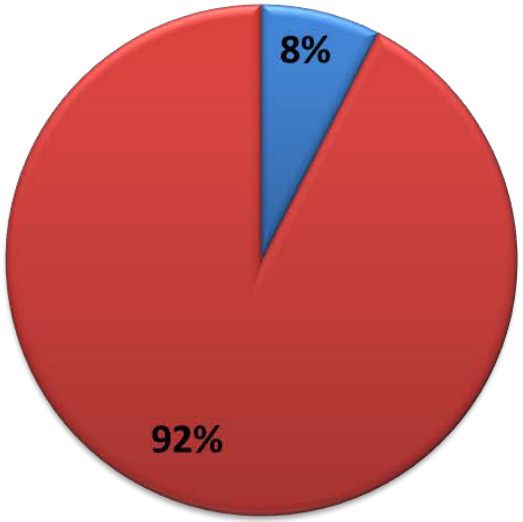
Nabelschnurblut für die verwandte (Familie) Nabelschnurbluttransplantation- Daten Düsseldorf- Häufigkeit und Indikationen

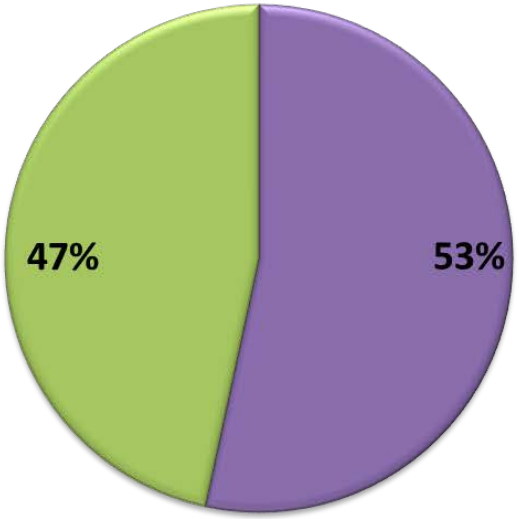
Verwandt	n= 444
transplantiert	n=16
HLA-identisch	26,8%
haploidentisch	51,3%
nicht identisch	21,9%



Leukämien / Lymphome	66%
Anämien	9%
Thalassämie	11%
sonstige Immundefekte	3%
genetische Erkrankungen	9%
sonstige Erkrankungen	2%

10.954* Nabelschnurbluttransplantationen in Europa allein, weltweit >35.000 (1988 – 2014) in 54 Ländern und 469* Transplantationszentren





Median age:
-children: 5y (0.02-17.9)
-adult: 42.8y (18.0-76.2)

*not including UCBT performed in US centres

eurocord
unique source NETCORD for stem cells

José-Carreras Stammzellbank Düsseldorf
Indikationen für die Stammzelltransplantation

Leukämien: AML, ALL, CML, CLL

Lymphome: HL, NHL

Genetische/Stoffwechselerkrankungen:

ß-Thalassämie, Sichelzellanämie, Fanconi-Anämie, Aplastische Anämie, hämophagozytische Lymphohistiozytose

Hurler´s Syndrom, Adenoleukodystrophie, Metachromatische Leukodystrophie, Niemann Pick, Infantile Neuronal Ceroid-Lipofuszinose

Schwerer kombinierter Immundefekt, Omenn Syndrom, Wiskott-Aldrich-Syndrom

Klinische Daten: allogene unverwandte CBT

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

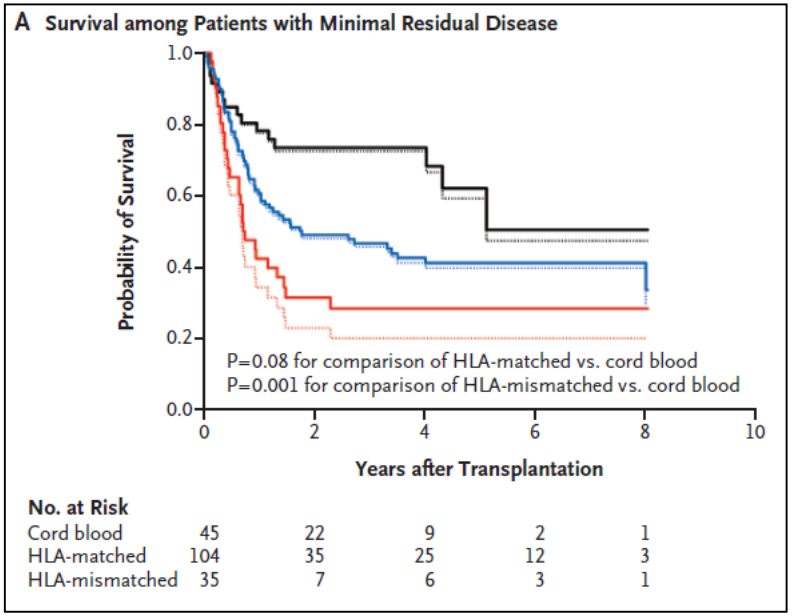
Cord-Blood Transplantation in Patients with Minimal Residual Disease

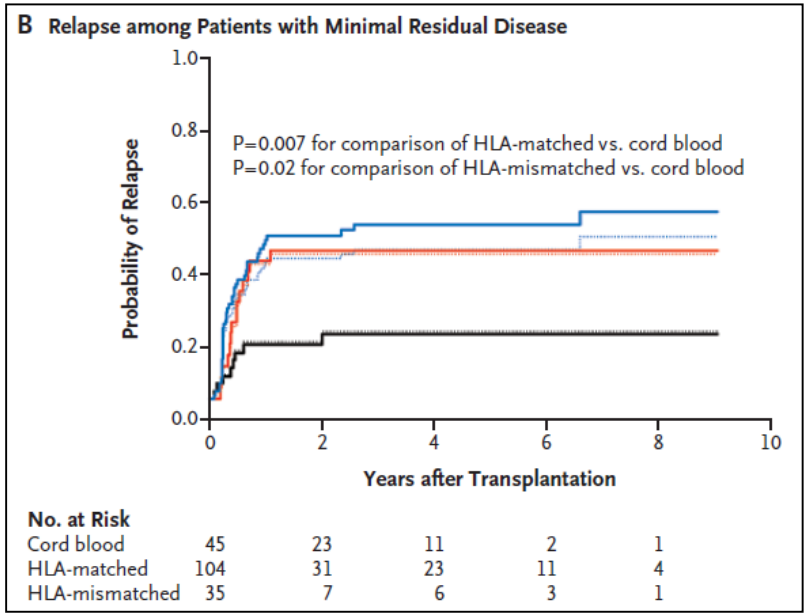
Filippo Milano, M.D., Ph.D., Ted Gooley, Ph.D., Brent Wood, M.D., Ann Woolfrey, M.D., Mary E. Flowers, M.D., Kristine Doney, M.D., Robert Witherspoon, M.D., Marco Mielcarek, M.D., Joachim H. Deeg, M.D., Mohamed Sorror, M.D., Ann Dahlberg, M.D., Brenda M. Sandmaier, M.D., Rachel Salit, M.D., Effie Petersdorf, M.D., Frederick R. Appelbaum, M.D., and Colleen Delaney, M.D.

Cord Blood — Adjusted; Unadjusted

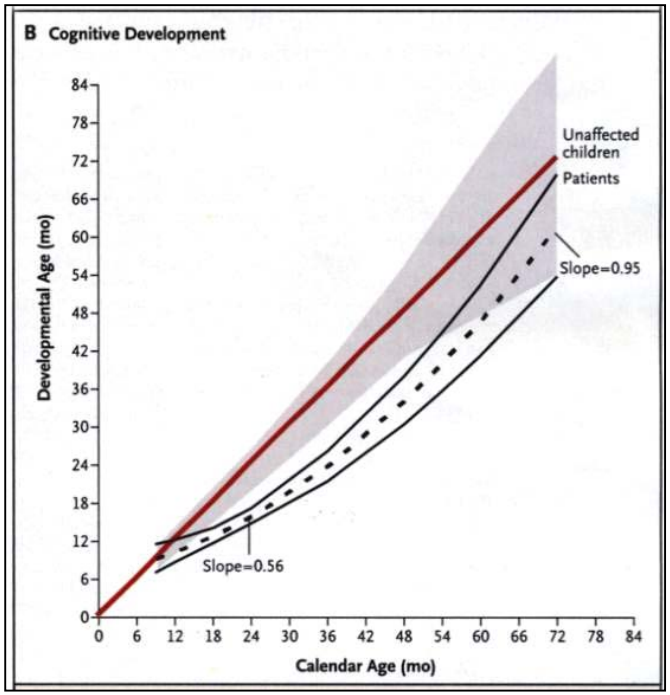
HLA-Matched — Adjusted; Unadjusted

HLA-Mismatched — Adjusted; Unadjusted





Auswirkung auf Entwicklung - MPS/Hurler bei Kindern- allogene Nabelschnurbluttransplantation



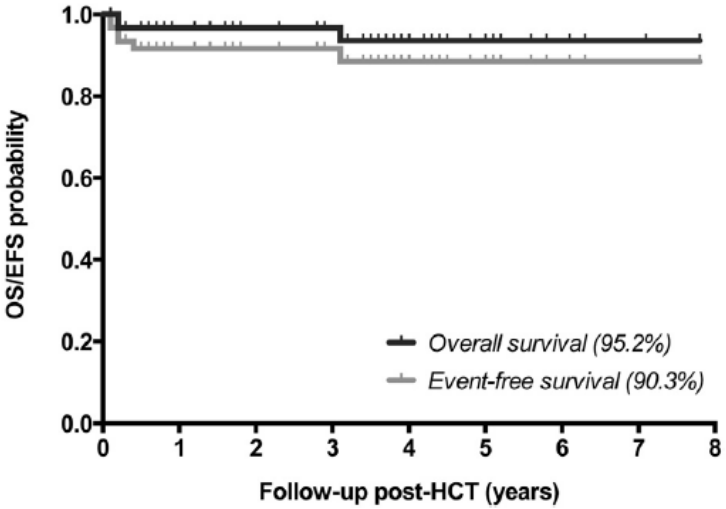


Figure 1. Overall survival and event-free survival.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cord-Blood Transplants from Unrelated Donors in Patients with Hurler's Syndrome

Susan L. Staba, M.D., Maria L. Escolar, M.D., Michele Poe, Ph.D., Young Kim, M.S., Paul L. Martin, M.D., Ph.D., Paul Szabolcs, M.D., June Allison-Thacker, R.N., Susan Wood, P.N.P., David A. Wenger, Ph.D., Pablo Rubinstein, M.D., John J. Hopwood, Ph.D., William Krivit, M.D., Ph.D., and Joanne Kurtzberg, M.D.

ELSEVIER

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Hematopoietic Cell Transplantation for Mucopolysaccharidosis Patients Is Safe and Effective: Results after Implementation of International Guidelines

Mieke Aldenhoven [1], Simon A. Jones [2], Denise Bonney [3], Roisin E. Borrill [3], Mary Coussons [3], Jean Mercer [2], Marc B. Bierings [1], Birgitta Versluys [1], Peter M. van Hasselt [4], Frits A. Wijburg [5], Ans T. van der Ploeg [6], Robert F. Wynn [3], Jaap Jan Boelens [1,*]

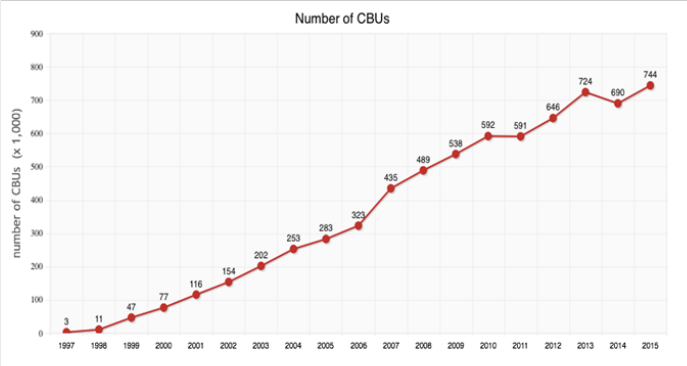
[1] Pediatric Blood and Marrow Transplantation Program, University Medical Center Utrecht, Utrecht, The Netherlands
[2] Willink Unit, Manchester Centre for Genomic Medicine, Central Manchester University Hospitals, University of Manchester, Manchester, United Kingdom
[3] Blood and Marrow Transplant Unit, Royal Manchester Children's Hospital, Manchester, United Kingdom
[4] Department of Metabolic Disorders, University Medical Center Utrecht, Utrecht, The Netherlands
[5] Department of Pediatrics and Amsterdam Lysosome Centre "Sphinx", University of Amsterdam, Amsterdam, The Netherlands
[6] Center for Lysosomal and Metabolic Diseases, Erasmus MC University Medical Center, Rotterdam, The Netherlands

Vergleich der gelagerten und verwendeten allogenen/autologen Nabelschnurblutpräparate weltweit

WMDA

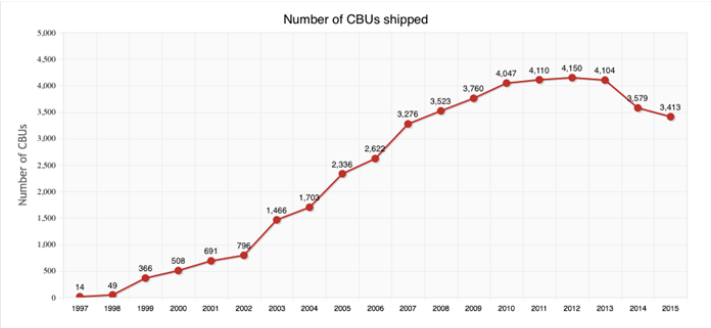
Allogenic unverwandte CB gelagert
Weltweit: **n = 744.000**

Autologe CB gelagert
Weltweit: **n > 4 Millionen Ende 2013)**



Allogene unverwandte CB transplantiert
Weltweit: **n = 44513 (6% Verwendungsrate)**

Autologe CB transplantiert
Weltweit: **n = 530 (0.01325% Verwendungsrate)**



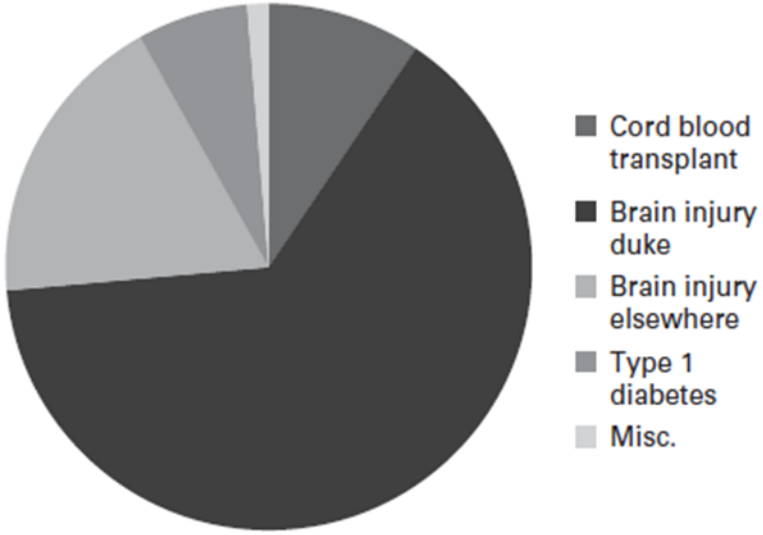
WMDA Annual Report 2015


Bone Marrow Transplantation (2015) 50, 1271 – 1278
© 2015 Macmillan Publishers Limited All rights reserved 0268-3369/15
www.nature.com/bmt

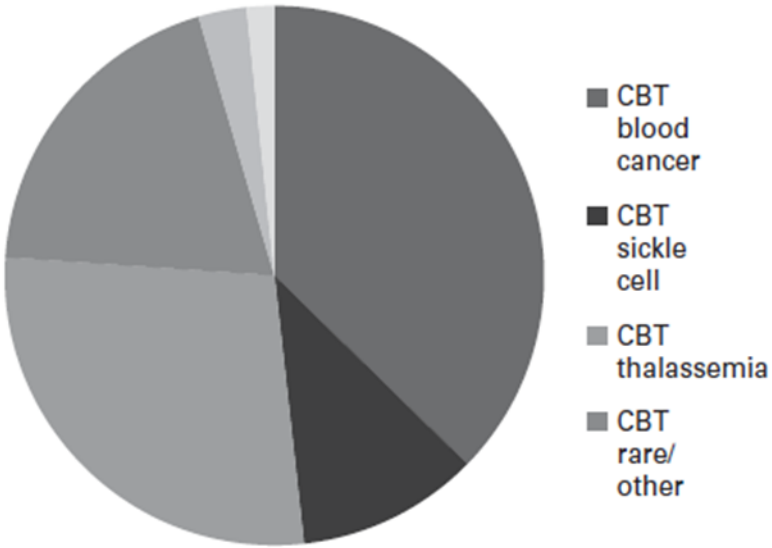
REVIEW
Umbilical cord blood donation: public or private?
KK Ballen[1], F Verter[2] and J Kurtzberg[3]

Ballen et al.2015

Indikationen für die allogene verwandte und autologe CBT in Kindern



Autologous UCBT from family banks.



Allogeneic UCBT from family banks.

Bone Marrow Transplantation (2015) **50,** 1271–1278

www.nature.com/bmt

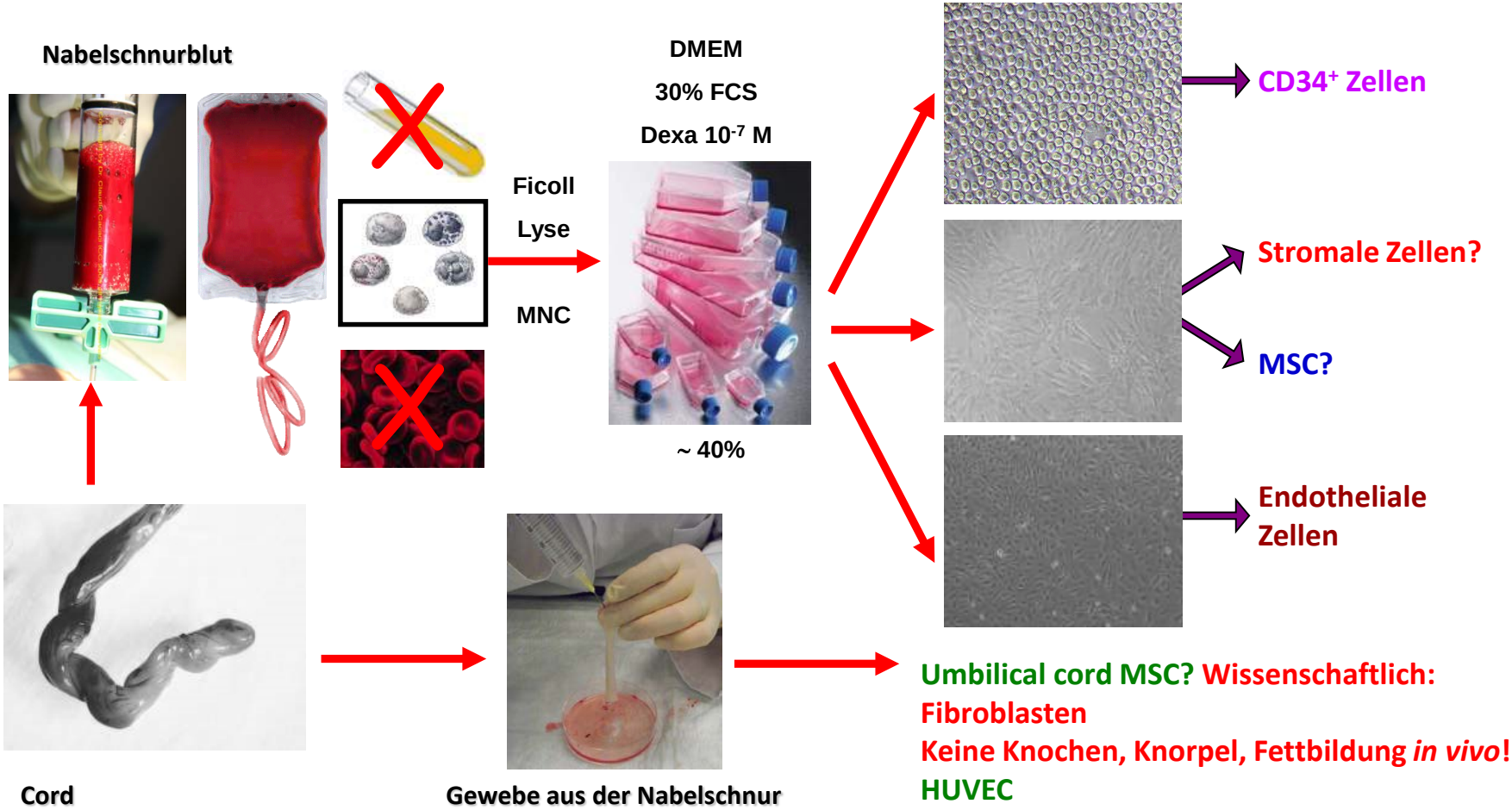
n= 485 (0.012% Verwendungsrate)

REVIEW

Umbilical cord blood donation: public or private?

KK Ballen[1], F Verter[2] and J Kurtzberg[3]

Nabelschnurblut: Vielfältige Zellen- Gewebe zur Regeneration



Umbilical cord MSC? Wissenschaftlich:
Fibroblasten
Keine Knochen, Knorpel, Fettbildung *in vivo*!
HUVEC

A New Human Somatic Stem Cell from Placental Cord Blood with Intrinsic Pluripotent Differentiation Potential

Gesine Kögler,[1] Sandra Sensken,[1] Judith A. Airey,[2] Thorsten Trapp,[1] Markus Müschen,[1] Niklas Feldhahn,[1] Stefanie Liedtke,[1] Rüdiger V. Sorg,[1] Johannes Fischer,[1] Claudia Rosenbaum,[3] Susanne Greschat,[3] Andreas Knipper,[1,4] Jörg Bender,[4] Özer Degistirici,[1,4] Jizong Gao,[5] Arnold I. Caplan,[5] Evan J. Colletti,[2] Graça Almeida-Porada,[6] Hans W. Müller,[3] Esmail Zanjani,[6] and Peter Wernet[1]

Erstmals 2004 beschrieben, höheres Differenzierungspotenzial im Vergleich zu BM-MSC

Allerdings: Teilweise Mischpopulation aus USSC und CB-MSC

Kögler et al. 2004, Kögler et al. 2015

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Phase 1 bis 3 Studien: Sonstige regenerative Therapien mit allogenem oder autologem Nabelschnurblut (und MSC aus Nabelschnurblut) - Beispiele

Approach	Disease	Investigator	Phase	current trial
Allogeneic UCB-Platelet Gel	UCB-deived Platelet Gel for Treatment of **Diabetic Foot Ulcers**	Royan Institute	Phase 2	NCT02134132
Allogeneic UCB-Platelet Gel	CB for the Treatment of **Diabetic Foot Ulcers**	Centro Nazionale Sangue, Italy	Phase 3	NCT02389010
Allogeneic UCB	**Autism Spectrum** Disorder	Duke University Kurtzberg, Joanne	Phase 2	NCT02847182
Allogeneic UCB	UCB Therapy for **Stroke**	Kim, Min Young	Phase 1	NCT01528436
Allogeneic UCB	UCB Therapy for Children with **Cerebral Palsy**	Kim, Min Young	Phase 2	NCT01639404
Allogeneic UCB	CB Infusion for **Ischemic Stroke**	Kurtzberg, Joanne Duke University	Phase 2	NCT03004976
Allogeneic UCB-MSC	Stem Cell Transplant for **Epidermolysis Bullosa**	Masonic Cancer Center, University of	Phase 2	NCT01033552
Allogeneic UCB-MSC	CB-derived MSC for **Degenerative Osteoarthritis/Articular Cartilage**	Medipost Co Ltd.	Phase 3	NCT01626677
Allogeneic UCB-MSC	UCB-derived MSC in **Regeneration of Sweat Glands and Body Repair**	Chinese PLA General Hospital	Phase 1	NCT02304562
Allogeneic UCB-MSC	UCB-derived-MSC for **Brochopulmonay Dysplasia**	Medipost America	Phase 2	NCT02381366
Autologous UCB	**Autism Spectrum** Disorder	Duke University Kurtzberg, Joanne	Phase 2	NCT02847182
Autologous UCB	**Autism Spectrum** Disorder	Duke University Kurtzberg, Joanne	Phase 2	NCT02847182
Autologous UCB	CB Cells for Neonatal Hypoxic **Ischemic Encephalopathy**	Cotten, Michael Duke University	Phase 2	NCT02612155
Autologous UCB	Moderate or Severe Hypoxic-**ischemic Encephalopathy** in Newborns	Cotten, Michael Duke University	Phase 2	NCT02612155
Autologous UCB	UCB Reinfusing in Children with **Cerebral Palsy**	Kurtzberg, Joanne Roberson Foundation	Phase 2	NCT01147653
Autologous UCB	UCB for Cardiac Regeneration in **Hypoplastic Left Heart Syndrom**	Mayo Clinic	Phase 1	NCT01856049
Autologous UCB	UCB for Infants with **Hypoplastic Left Heart Syndrom**	Cotten, Michael Duke University	Phase 1	NCT01445041
Autologous UCB	CB Infusion in Children with **Cerebral Palsy**	Hanyang University Seoul Hospital	Phase 2	NCT02866331
Autologous UCB	CB Stem Cell Infusion for the Treatment of **Cerebral Palsy** in Children	Augusta University Carroll, James E.	Phase 2	NCT01072370
Autologous UCB	UCB to Treat Pediatic **Traumatic Brain Injury**	Cox, Charles University of Texas	Phase 2	NCT01251003

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

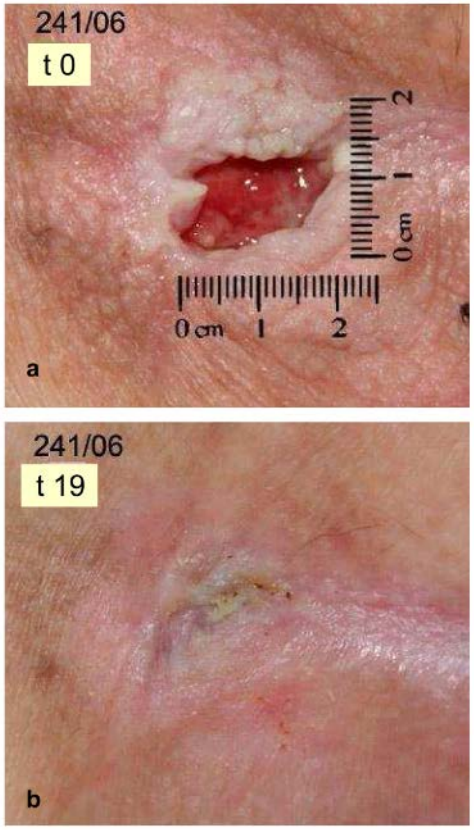
José Carreras Stammzellbank

Biologicals

Volume 39, Issue 2, March 2011, Pages 73–80

Treatment of recalcitrant ulcers with allogeneic platelet gel from pooled platelets in aged hypomobile patients

N. Greppi[a], L. Mazzucco[b], G. Galetti[c], F. Bona[b], E. Petrillo[a], C. Smacchia[a], E. Raspollini[a], P. Cossovich[c], R. Caprioli[c], P. Borzini[b], P. Rebulla[d], M. Marconi[a]



ig. 3. IV stage ulcer from patient no. 7 before treatment (a, $t = 0$) and after 19 weeks f treatment with PG (b, $t = 19$).

Alle Anwendungsmöglichkeiten zur neuronalen Regeneration
nur parakrin!
Obwohl: Neuronale Differenzierung aus Nabelschnurblut nur *in vitro*

Nach Induktion in XXL-Medium „neuro-ähnlichen Phänotyp“

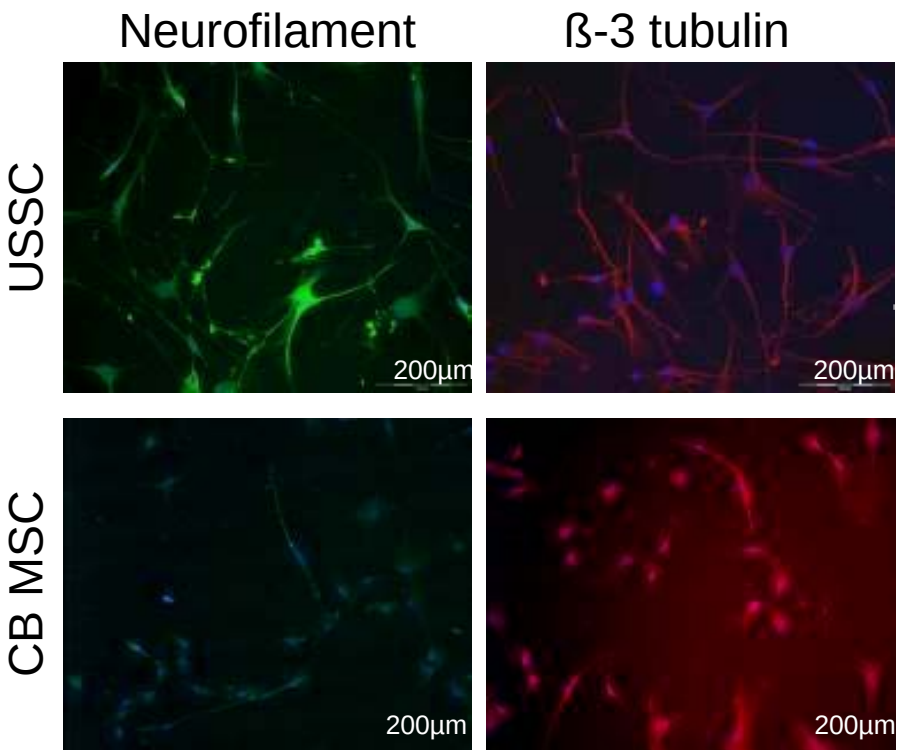
STEM CELLS AND DEVELOPMENT 17:221–232 (2008)

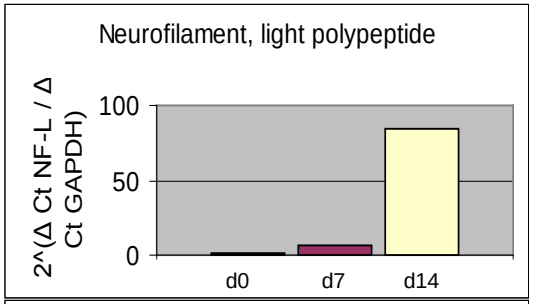
DOI: 10.1089/scd.2007.0118

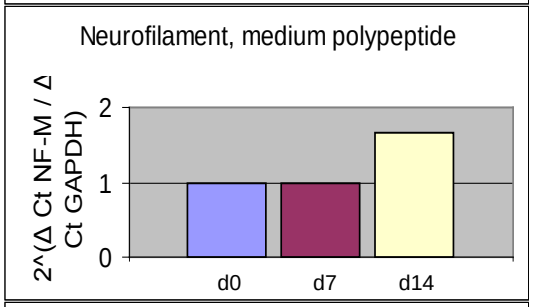
Original Research Report

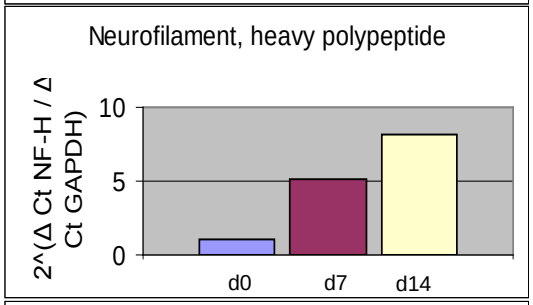
Unrestricted Somatic Stem Cells from Human Umbilical Cord Blood Can be Differentiated into Neurons with a Dopaminergic Phenotype

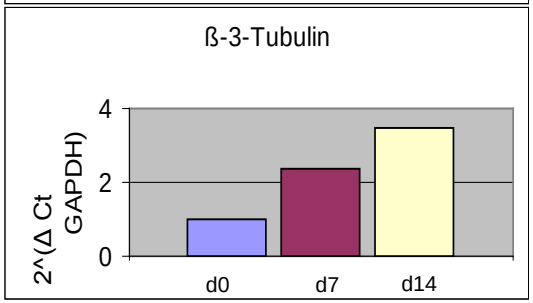
SUSANNE GRESCHAT,[1] JESSICA SCHIRA,[1] PATRICK KÜRY,[1] CLAUDIA ROSENBAUM,[1] MARIA ANGELICA DE SOUZA SILVA,[2] GESINE KÖGLER,[3] PETER WERNET,[3] and HANS WERNER MÜLLER[1]



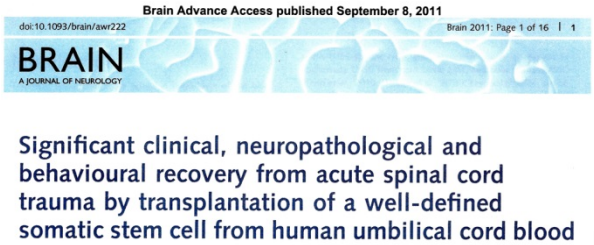






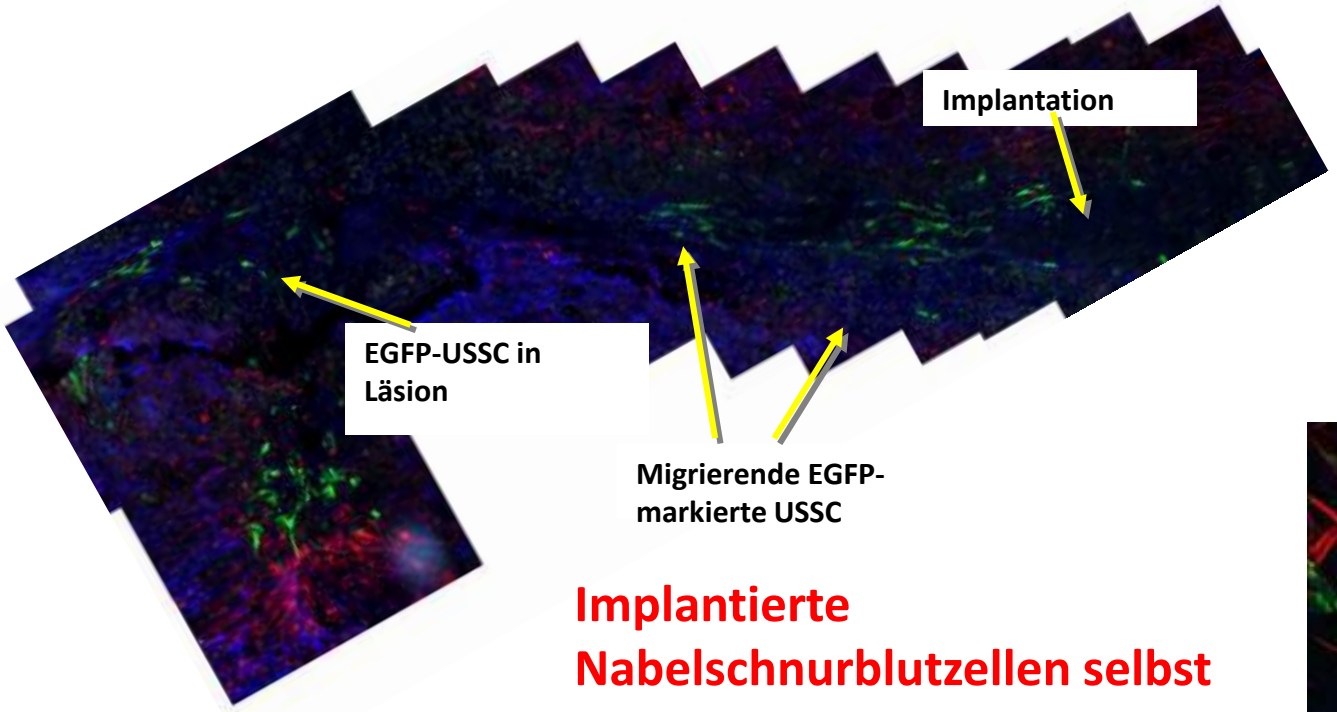


Unterstützung der neuronalen Regeneration (*in vivo*)

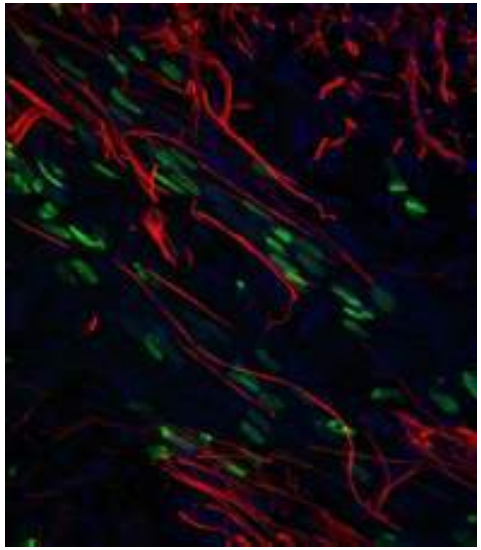

Brain Advance Access published September 8, 2011
doi:10.1093/brain/awr222 Brain 2011: Page 1 of 16 | 1
BRAIN
A JOURNAL OF NEUROLOGY

Significant clinical, neuropathological and behavioural recovery from acute spinal cord trauma by transplantation of a well-defined somatic stem cell from human umbilical cord blood

Implantation von USSC nach Rückenmarksverletzung führt zu Migration in Richtung Läsionsstelle (Tiermodell Ratte)



Implantierte Nabelschnurblutzellen selbst differenzieren nicht !



Neurofilament-positive regenerierende Axone (rot) und USSC (grün) 3 Wochen nach Läsion und Implantation, J. Schira, Labor Prof. Müller).

Charakterisierung eines regenerativen Phänotyps

Xenogene and allogene MSC from CB showing in neuroregenerative disorders anti-apoptotic mechanism (Chen 2013, Dasari 2008, 2009).

Anti-apoptotic “prosurvival“ effects via the Akt-Signaling pathway? (Franke 2008, Gottlob 2001, Manning 2002).

Akt signaling pathway is involved in the inhibition of neuronal apoptosis

Anti-apoptotic characteristics of a cell population is relevant for degenerative disorders

Potential candidate genes in stromal cells:

Gene Set Enrichment Analysis“ (GSEA): 6 genes of the mTOR signaling pathway could be identified (e.g. EIF4EBP1, PGF, DDIT4, RPS6KA2 und VEGFA)

Allogenes unverwandtes Nabelschnurblut zur Behandlung von Schlaganfall bei Kindern

6 *Y. A. Romanov et al.*

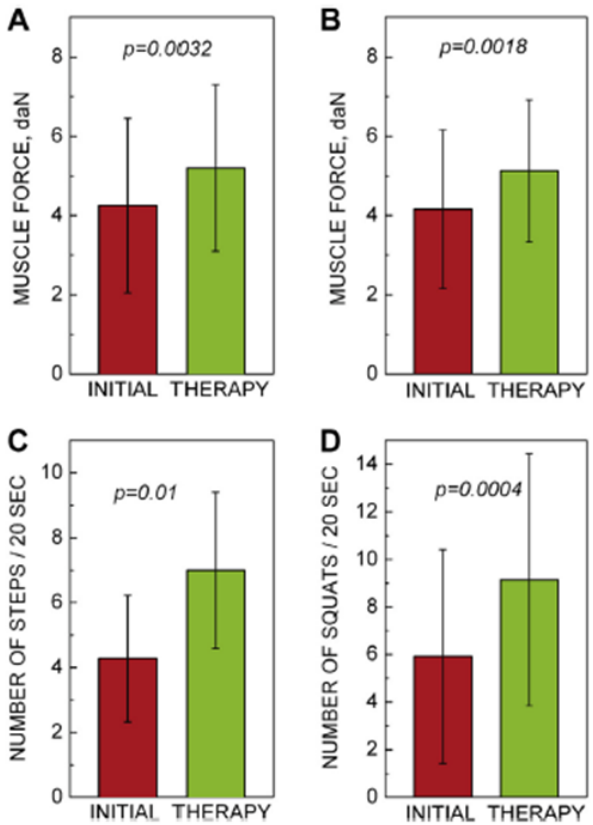


Figure 3. Effects of UCB cell therapy on physical development indices. A and B, results of hand dynamometry (A, right hand; B, left hand); C and D, number of steps and squats performed by patients independently during 20 seconds, respectively. Data are presented as mean ± SD for 15 patients (aged 4.6–7.5 years) with the ability to hold and squeeze the dynamometer and/or walk on one's own before initiating treatment.

Cytotherapy, 2015; 0: 1–10
International Society for Cellular Therapy ISCT

Human allogeneic AB0/Rh-identical umbilical cord blood cells in the treatment of juvenile patients with cerebral palsy

YURY A. ROMANOV[1], OLEG P. TARAKANOV[2], SERGEY M. RADAEV[2], TAMARA N. DUGINA[2], SVETLANA S. RYASKINA[2], ANNA N. DAREVSKAYA[2], YANA V. MOROZOVA[2], WILLIAM A. KHACHATRYAN[3], KONSTANTIN E. LEBEDEV[3], NELLI S. ZOTOVA[4], ANNA S. BURKOVA[4], GENNADY T. SUKHIKH[4] & VLADIMIR N. SMIRNOV[1]

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Study of Allogeneic Umbilical Cord Blood Infusion for Adults With Ischemic Stroke - PHASE 2

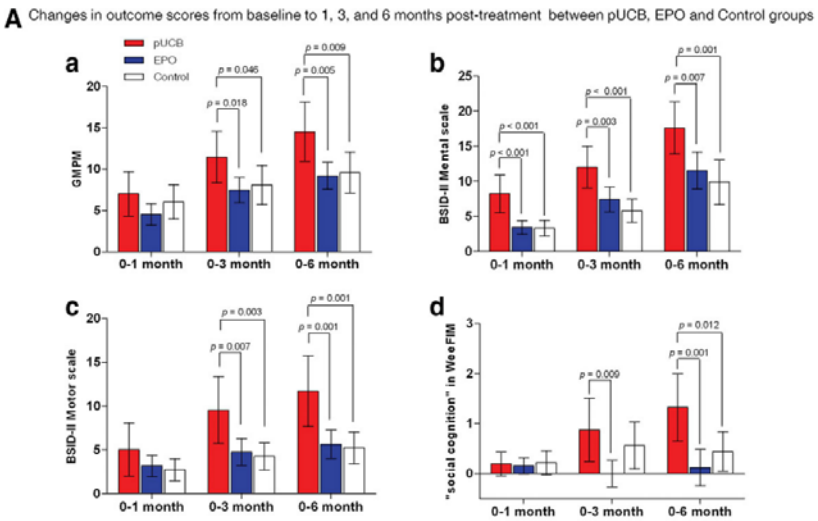
Approach	Disease	Investigator	Phase	current trial
Allogeneic UCB	Study of Allogeneic Umbilical Cord Blood Infusion for Adults With Ischemic Stroke	Kurtzberg, Joanne Duke University	Phase 2	NCT03004976

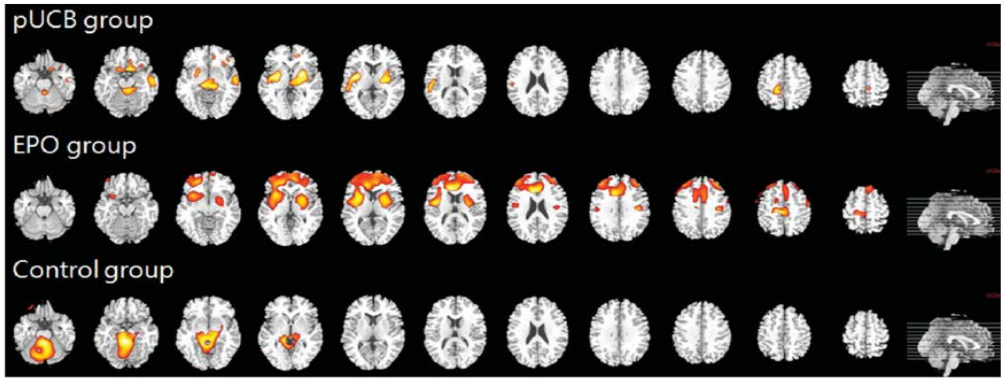
The primary objective of this **Phase 2 Study** is to determine the efficacy of a single intravenous infusion of unrelated donor umbilical cord blood (UCB) for improving functional outcomes in patients with ischemic stroke. Eligible subjects will receive an intravenous infusion of UCB or placebo 3-10 days following stroke. Subjects will not receive immunosuppressive or myeloablative medications prior to the infusion. Subjects will be followed for one year post infusion for safety and efficacy. Assessments will examine safety and tolerability of the infusion, change in neurological symptoms, change in quality of life, and emotional and cognitive status. Assessments will occur at 24 hours post infusion, and at 30, 90, 180 and 365 days post infusion.

Study Status:	This study is currently recruiting participants.
Estimated Study Completion Date:	April 2020
Estimated Primary Completion Date:	April 2019 (Final data collection date for primary outcome measure)

Allogenes unverwandtes Nabelschnurblut zur Behandlung von Zerebralen Hirnschäden bei Kindern, jetzt Phase 2 - Kinder und junge Erwachsene 6 Monate- 20 Jahre

Approach	Disease	Investigator	Phase	current trial
Allogeneic UCB	UCB Therapy for Children with **Cerebral Palsy**	Kim, Min Young	Phase 1	NCT01639404





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TRANSLATIONAL AND CLINICAL RESEARCH

Umbilical Cord Blood Therapy Potentiated with Erythropoietin for Children with Cerebral Palsy: A Double-blind, Randomized, Placebo-Controlled Trial

KYUNGHOON MIN,[a] JUNYOUNG SONG,[a] JIN YOUNG KANG,[a] JOOYEON KO,[a] JU SEOK RYU,[a] MYUNG SEO KANG,[b,c] SU JIN JANG,[d] SANG HEUM KIM,[e] DOYEUN OH,[f] MOON KYU KIM,[g] SUNG SOO KIM,[h] MINYOUNG KIM[a]

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HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

STEM CELLS TRANSLATIONAL MEDICINE

CORD BLOOD

Autologous Cord Blood Infusions Are Safe and Feasible in Young Children with Autism Spectrum Disorder: Results of a Single-Center Phase I Open-Label Trial

GERALDINE DAWSON,[a] JESSICA M. SUN,[b] KATHERINE S. DAVLANTIS,[a] MICHAEL MURIAS,[a,c] LAUREN FRANZ,[a] JESSE TROY,[b] RYAN SIMMONS,[b] MAURA SABATOS-DEVITO,[a] REBECCA DURHAM,[b] JOANNE KURTZBERG[b]

Key Words. Autism spectrum disorder • Autologous umbilical cord blood • Cell therapy

Authored by a member of CORD BLOOD ASSOCIATION

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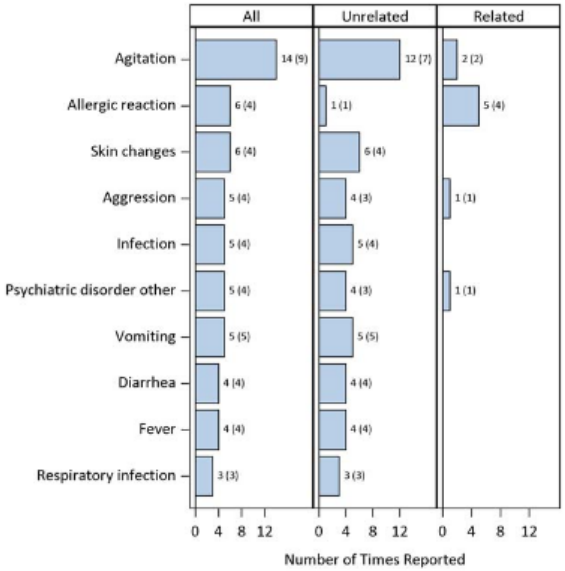

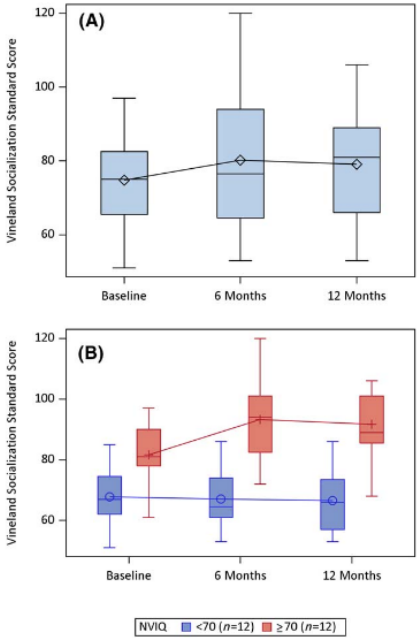

Figure 2. Vineland Adaptive Behavior Scales-II (VABS-II) Socialization Standard Score. **(A)**: Distribution of VABS-II Socialization Standard Score in all participants over time. **(B)**: Distribution of VABS-II Socialization Score stratified by nonverbal intelligence quotient.

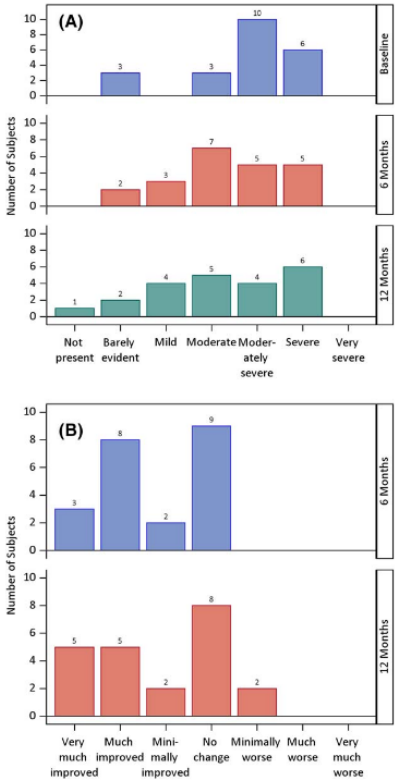

Figure 3. Global Impression Scale (GCI). **(A)**: CGI-Severity over time. **(B)**: CGI-Improvement over baseline as assessed at 6 and 12 months.

Table 4. Raw and corrected *p* values for tests of the null hypothesis of No change over time in behavioral outcomes

	Baseline to 6 months		6 to 12 months	
Outcome measure	**Raw *p* value**	**FDR *p* value**	**Raw *p* value**	**FDR *p* value**
EOWPVT Raw Score	.0001	.0009	.0011	.0059
CGI-I	.0010	.0045	.0013	.0059
VABS Communication Standard Score	.0020	.0060	.4590	.8262
PDDBI Autism Composite T-Score[a]	.0040	.0090	.4300	.8262
VABS Adaptive Behavior Composite	.0070	.0126	.6870	.8833
VABS Socialization Standard Score	.0160	.0240	.6020	.8833
CGI-S	.0220	.0283	.3750	.8262
VABS Daily Living Standard score	.4600	.5175	.9999	.9999
VABS Motor Function Standard Score	.7880	.7880	.9907	.9999

[a]*p* values for the PDDBI are for baseline to 3 months and 3 to 12 months.
Abbreviations: CGI-I/S, Clinical Global Impression—Improvement/Severity; EOWPVT, Expressive One-Word Picture Vocabulary Test-4; FDR, False Discovery Rate; PDDBI, Pervasive Developmental Disorder Behavior Inventory; VABS, Vineland Adaptive Behavior Scales-II.

Nabelschnurblut allogen

- Etabliert > 70 hämatologische Indikationen ✓
- MSC/USSC Stromazellen: GMP-grade Knochen, Knorpelregeneration Nabelschnurblut MSC ✓
- (nicht Fibroblasten aus der Nabelschnur!)

Nabelschnurblut allogen

- Thrombozyten-Gel ✓ Plasmaaugentropfen ? ✓
- Unique anti-apoptotische Aktivität (Unterstützung der neuronalen Regeneration/ "parakrine Mechanismen")?
- **Schlaganfall, Zerebrale Hirnschäden, Autismus?**
- Hoher Level an DNA-repair ✓

Biologische Vorteile von Nabelschnurblut im Vergleich zu adultem Blut/Knochenmark

- Junges Stammzellkompartment
- Hohe Proliferation, lange Telomere
- Verfügbar – Kein Risiko für den Spender
- Ethische Fragen?
- Infektionserkrankungen CMV, EBV selten
- Immunologische Unreife

Exzellente Quelle zur Reprogrammierung- IPS

Perspektiven

- Nabelschnurblut –vielfältige Spender vorhanden
- Nabelschnurblut schützt vermehrt gegen Leukämisches Rezidiv

- Regenerative Medizin und zelluläre Therapien?

- Steigende Nachfrage zur Herstellung anderer zellulärer Produkte aus Nabelschnurblut
- Aktuelle und geplante Studien:
- Schlaganfall, zerebrale Hirnschäden, Autismus

UKD Universitätsklinikum Düsseldorf

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Tag der offenen Tür in der José Carreras Stammzellbank am 15. November 2017

www.WorldCordBloodDay.org; www.stammzellbank.de