BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Mueller, Martin

eRA COMMONS USER NAME (credential, e.g., agency login): MARTINMULLER

POSITION TITLE: Medical Director and Senior Registrar Physician (Bern), Visiting Assistant Professor (Yale)

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Wroclaw Medical University, Poland	MD	07/2002	Medicine
Ruhr Universität Bochum, Germany	MD	12/2002	Medicine
Ruhr Universität Bochum, Germany		10/2004	Obstetrics & Gynecology, Internship
MHK Neuwied, Germany		11/2008	Obstetrics & Gynecology, Residency and Medical Specialist
University Hospital Bern, Switzerland		01/09-present	Obstetrics & Gynecology, Maternal Fetal Medicine, Neuroscience
Yale University School of Medicine, USA		06/2013- present	Neuroscience

A. Personal Statement

I am an obstetrician and neuroscientist. My activities span direct patient care and research. My career in medicine has focused on basic research of hypoxic-ischemic encephalopathy with special emphasis on therapeutic approaches to salvage brain tissue. I have a broad background in pathophysiology of brain injuries, with specific training and expertise in molecular techniques to underpin the mechanism`s related changes. During the last years, I have intensively evaluated the neuroprotective activity of Estrogen, Wharton`s jelly derived stem cells, and synthetic PreImplantation Factor (sPIF) as therapeutic options for brain injuries. We have adopted an animal model of encephalopathy of prematurity and successfully used estrogen and stem cell transplantation. Additionally we have focused on evaluation of sPIF as a therapeutic option for immature infants at risk. sPIF has unique immune modulatory properties and was successfully tested in vitro and in vivo.

In the last 5 years I have been collaborating with Drs. Paidas (Yale University School of Medicine) intensively. We tested sPIF in clinically relevant murine brain injury models. Additionally, we focused on the diagnostic and therapeutic applications of sPIF in acute radiation injury animal model and chronic neurodegeneration models. Further I collaborated with Dr. Huang (Yale University School of Medicine) and investigated the role of non-coding RNAs in metabolic and inflammation related diseases such as diabetes and endometriosis. My recent collaboration with Dr. Bordey (Yale University School of Medicine) has generated preliminary results showing that sPIF targets endogenous stem cells for repair after brain injury.

1. Schoeberlein A*, **Mueller M***, Reinhart U, Sager R, Messerli M, Surbek DV. Homing of placenta-derived mesenchymal stem cells after perinatal intracerebral transplantation in a rat model. Am J Obstet Gynecol. 2011 Sep;205(3):277.e1-6. *both authors contributed equally to this work
2. **Müller M,** Middelanis J, Meier J, Surbek DV, Berger R. 17β-Estradiol protects 7-day old rats from acute brain injury and reduces the number of apoptotic cells. Reproductive Sciences Epub.2012/08/10
3. **Mueller M,** Zhou J, Gao Y, Wu F, Schoeberlein A, Surbek D, Barnea E, Paidas M, Huang Y. Preimplantation factor (PIF) promotes neuroprotection by targeting microRNA let-7. Proc Natl Acad Sci USA. 2014 Sep 23;111(38):13882-7
4. **Mueller M,** Schoeberlein A, Zhou J, Joerger-Messerli M, Bordey A, Surbek D, Barnea E, Paidas M. PreImplantation Factor bolsters neuroprotection via modulating Protein Kinase A and Protein Kinase C signaling. (Cell Death and Differentiation 05/2015)
5. Oppliger B, Joerger-Messerli M, **Mueller M**, Reinhart U, Schneider P, Surbek DV, Schoeberlein A. Intranasal Delivery of Umbilical Cord-Derived Mesenchymal Stem Cells Preserves Myelination in Perinatal Brain Damage. Stem Cells Dev. 2016 Aug 15;25(16):
6. Shainer R, Almogi-Hazan O, Berger A, Hinden L, **Mueller M**, et al. PreImplantation factor (PIF) therapy provides comprehensive protection against radiation induced pathologies. Oncotarget. 2016 Jul 16;

B. Positions and Honors

Positions and Employment

2002–2004	Resident Physician, Department of Obstetrics and Gynecology, Ruhr Universität Bochum, Bochum, Germany (Prof. A. Jensen)
2004–2008	Resident Physician and Senior Registrar, Department of Obstetrics and Gynecology, MHK Neuwied, Germany (Prof. R. Berger)
2008	Board Certification in Obstetrics and Gynecology
2013	Subspeciality title (FMH) "Obstetrics and Feto-Maternal Medicine"
2013-2014	Postdoctoral Associate, Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale University School of Medicine, New Haven, CT, USA (Prof. M. Paidas)
2009-present	Senior Registrar Physician, Department of Obstetrics and Gynecology, University Hospital Bern, Bern, Switzerland (Prof. D. Surbek)
2015-present	Visiting Assistant Professor, Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale University School of Medicine, New Haven, CT, USA
08/2015-present	Medical Director of the Outpatient Clinic, Department of Obstetrics and Gynecology, University Hospital Bern, Bern, Switzerland

Other Experience and Professional Memberships

2007-present	Arbeitsgemeinschaft für MaternoFetale Medizin (AGMFM of DGGG)
2007-present	Deutsche Gesellschaft für Ultraschall Medizin (DEGUM)
2009-present	International Society of Ultrasound in Obstetrics and Gynecology (ISUOG)
2009-present	Lecturer in Obstetrics and Gynecology, Bern University of Applied Sciences
2010-present	Deutsche Gesellschaft für Perintal- und Geburtsmedizin Medizin (DGPGM)
2010-present	Schweizerische Gesellschaft für Ultraschall in der Medizin (SGUM)
2012	Tutor at the 18th International Society for the Study of Hypertension in Pregnancy

Honors

2005	President's Presenter Award (Society for Gynecologic Investigation), Los Angeles
2005	Research Award, German Society of Perinatal Medicine (DGPM), Berlin
2011	Award of Research Excellence (Society of Materno Fetal Medicine), San Francisco
2011	Research Award, Society of Gynecology and Obstetrics (SGGG), Lugano
2012	Research, Society of Gynecology and Obstetrics (SGGG), Interlaken
2012	Bayer Award 2012 for the best manuscript in Obstetrics and Gynecology, Interlaken.

2014	Selected trainee of the “Training in Neurotherapeutics Discovery and Development for Academic Scientists, 2014”. National Institute of Neurological Disorders and Stroke and the NIH Blueprint for Neuroscience Research.
2015	Venia docendi (University of Bern, Switzerland)
2015	Selected trainee of the GLOBE program (Global Leadership in Obstetrics and Gynecology), London, UK

C. Contribution to Science

My research career in medicine has focused on reducing perinatal morbidity and mortality with emphasis on therapeutic approaches to salvage hypoxic-ischemic encephalopathy. My diligence, enthusiasm, and thirst for knowledge are based on the simple question of a mother after a complicated delivery: “Can you help my baby?” Unfortunately, the current therapeutic options to reduce the burden of perinatal brain injury are lacking.

1. Maternal aspects of perinatal morbidity and mortality

Caesarean section (CS) rates have risen over the past two decades. Given CS`s risks and the high CS rate in our institution we aimed to identify contributing factors. We noted a shift towards a high-risk population with biggest contributors to high CS rates: previous uterine scar and preterm delivery. As a consequence we implemented interventions aiming to reduce CS rates. Another factor contributing to neonatal morbidity and mortality are group B streptococci (GBS), which may lead to early onset neonatal sepsis. As the source of colonization for neonates is the GBS-positive mother and intrapartum antibiotics reduce the vertical transmission we conducted a prospective study to evaluate an onsite PCR based test. To further assess proper antibiotic prophylaxis we evaluated GBS serotype distribution and the rates of antibiotics resistance as well. We concluded that the PCR-based test is an attractive strategy to reduce neonatal GBS sepsis and penicillin is the antibiotic of choice for intrapartum prophylaxis.

a. **Mueller M**, Kolly L, Baumann M, Imboden S, Surbek D. Analysis of Caesarean Section Rates Over Time in a Swiss Single Center Using a 10 Group Classification System. Swiss Med Wkly. 2014; 144:w13921
b. **Mueller M**, Henle A, Droz S, Kind A, Rohner S, Baumann M, Surbek DV. Intrapartum Detection of Group B Streptococci Colonization by Rapid PCR-Test on Labor Ward. Eur J Obstet Gynecol Reprod Biol. 2014 May;176:137-41.
c. Fröhlicher S, Reichen G, **Mueller M**, Surbek D, Droz S, Spellerberg B, Sendi P. Serotype Distribution and Antimicrobial Susceptibility of Group B Streptococcus in Pregnant Women: Results from a Swiss Tertiary Centre. Swiss Med Wkly. 2014; 144:w13935
d. Christmann-Schmid C, Raio L, Scheibner K, **Mueller M**, Surbek D. Back to "once a caesarean: always a caesarean"? A trend analysis in Switzerland. Arch Gynecol Obstet. 2016 Nov;294(5):905-910.

2. Neonatal aspects of perinatal morbidity and mortality

Hypoxic-ischemic (HI) encephalopathy is a major cause of neonatal death and long-term disability and successful therapeutic approaches are lacking, so we evaluated therapeutic approaches to reduce this burden.

Stem Cells: We focused on stem cells as stem cell transplantation may lead to the regeneration and/or repair of injured neuronal tissues. Additionally stem cells derived from the placental tissue (namely: amnion, chorion, or the umbilical cord) are an easily accessible source without ethical controversies. Thus we decided to test the neuroregenerative capacity of placenta stem cells. We evaluated stem cells derived from preeclamptic and uncomplicated pregnancies as preeclampsia is associated with perinatal brain injury. Although stem cells from preeclamptic pregnancies expressed different patterns of surface markers, stem cells from both preeclampsia and uncomplicated groups differentiated preferably into stem/progenitor (Nestin+) and neuronal cells (Tuj-1+). Next, we focused on Wharton`s Jelly derived mesenchymal stem cells (WJ-MSCs), which are derived from the umbilical cord. WJ-MCs are easy available after birth, efficacious, and have regenerative and immunomodulatory capacities. First we assessed the neuroregenerative capacity of preterm versus term deliveries derived WJ-MSCs. Indeed WJ-MSCs expressed several cellular markers independent of gestational age. To further elucidate WJ-MSC`s capacity as cellular graft we compared cells derived from preeclamptic and gestational age matched deliveries as well. Interestingly WJ-MSCs from preeclamptic deliveries seem to be more committed to neuroglial differentiation. Together we concluded that both term and preterm derived placental stem cells are suitable as

cell grafts and might be used as a therapeutic approach. Thus, we transplanted WJ-MSCs using intracerebral injection in a rat model of HI encephalopathy. We detected graft cells in the brain ventricle shortly after injection. Further these cells migrated throughout the ventricular system into the periventricular white matter.

a. Portmann-Lanz CB, Baumann MU, **Mueller M,** Wagner AM, Weiss S, Haller O, Sager R, Reinhart U, Surbek DV. Neurogenic characteristics of placental stem cells in preeclampsia. Am J Obstet Gynecol. 2010 Oct;203(4):399.e1-7
b. Schoeberlein A*, **Mueller M*,** Reinhart U, Sager R, Messerli M, Surbek DV. Homing of placenta-derived mesenchymal stem cells after perinatal intracerebral transplantation in a rat model. Am J Obstet Gynecol. 2011 Sep;205(3):277.e1-6. *both authors contributed equally to this work
c. Messerli M, Wagner A, Sager R, **Mueller M,** Baumann M, Surbek DV, Schoeberlein A. Stem cells from umbilical cord Wharton`s jelly: Ideal cell graft for the treatment of brain injury in preterm birth? Reproductive Sciences, 2013 1933719113488443, first published on May 13.
d. Joerger-Messerli M, Bruehlmann E, Bessire A, Wagner A, **Mueller M,** Surbek D, Schoeberlein A. Preeclampsia enhances neuroglial marker expression in umbilical cord Wharton's jelly-derived mesenchymal stem cells. The Journal of Maternal-Fetal & Neonatal Medicine 2014 May 7.
e. Oppliger B, Joerger-Messerli M, **Mueller M**, Reinhart U, Schneider P, et al. Intranasal Delivery of Umbilical Cord-Derived Mesenchymal Stem Cells Preserves Myelination in Perinatal Brain Damage. Stem Cells Dev. 2016 Aug 15;25(16):1234-42.
f. **Mueller M**, Wolfs TG, Schoeberlein A, Gavilanes AW, Surbek D, et al. Mesenchymal stem/stromal cells-a key mediator for regeneration after perinatal morbidity?. Mol Cell Pediatr. 2016 Dec;3(1):6

3. 17β-Estradiol:

In parallel to our stem cell studies we tested 17β-Estradiol (E2) in our rat model of HI encephalopathy. Notably, during pregnancy fetuses are exposed to high levels of E2 and premature birth leads to E2 deprivation. Treatment with E2 protected newborn rat brains in terms of both microscopic cell injury and apoptosis compared to injured not treated animals.

a. **Mueller M,** Middelanis J, Meier J, Surbek DV, Berger R. 17β-Estradiol protects 7-day old rats from acute brain injury and reduces the number of apoptotic cells. Reproductive Sciences Epub.2012/08/10

4. PreImplantation Factor:

Secreted from developing embryos, PreImplantation Factor (PIF) can be detected in the maternal circulation during pregnancy. Thus, PIF has been implicated in promoting embryo implantation through modulating maternal immune tolerance. Consistent with the immune function, a synthetic PIF analog (sPIF) of 15 amino acids (MVRIKPGSANKPSDD) that was subcutaneously administrated was able to both reverse and prevent paralysis through inhibiting neuroinflammation in a murine model of experimental autoimmune encephalomyelitis. We hypothesized that sPIF may prevent/reduce HI encephalopathy as well.

Dysfunction and loss of neurons are the major characteristics of central nervous system (CNS) disorders that include stroke, multiple sclerosis, and Alzheimer`s disease. Activation of the Toll like receptor 7 by extracellular let-7, a highly expressed microRNA in the CNS, induces neuronal cell death. We showed that sPIF inhibited the biogenesis of let-7 in both neuronal and immune cells of the mouse. sPIF destabilized KSRP, a key microRNA processing protein, in a Toll-like Receptor 4 (TLR4) -dependent manner, leading to decreased production of let-7. Furthermore, subcutaneous administration of sPIF into neonatal rats following HI brain injury robustly rescued cortical volume and number of neurons while decreasing detrimental glial response, consistent with diminished levels of KSRP and let-7 in sPIF-treated brains.

In search of additional mechanisms, we focused on cyclic AMP-dependent protein kinase (PKA) and calcium-dependent protein kinase (PKC). PKA/PKC signaling is downstream of TLR4 and TLR4 was required for sPIF induced neuroprotective effects. Notably, PKAs/PKCs are important signaling molecules in a variety of cellular functions, including cell growth and differentiation, neuronal plasticity and cellular response to stress. We showed that sPIF activates PKA/PKC signaling both in vitro and in vivo. Using a clinically relevant rat newborn brain injury model, we demonstrate that sPIF is able to reduce cell death, reverse neuronal loss and restore proper cortical architecture. Further, activation of PKA/PKC signaling leads to increased phosphorylation of major neuroprotective substrates GAP-43, BAD and CREB. Phosphorylated CREB in turn facilitates expression of *Gap43*, *Bdnf* and *Bcl2,* which are known to have important roles in regulating neuronal growth, survival and

remodeling. As is the case in sPIF-mediated let-7 repression, we provide evidence that sPIF-mediated PKA/PKC activation is dependent on TLR4 expression. Thus, we proposed that sPIF imparts neuroprotection via multiple mechanisms at multiple levels downstream of TLR4. Given the recent FDA fast-track approval of sPIF for clinical trials, its potential clinical application for treating other CNS diseases can be envisioned.

a. **Mueller M,** Zhou J, Gao Y, Wu F, Schoeberlein A, Surbek D, Barnea E, Paidas M, Huang Y. Preimplantation factor (PIF) promotes neuroprotection by targeting microRNA let-7. Proc Natl Acad Sci USA. 2014 Sep 23;111(38):13882-7
b. **Mueller M,** Schoeberlein A, Zhou J, Joerger-Messerli M, Bordey A, Surbek D, Barnea E, Paidas M. PreImplantation Factor bolsters neuroprotection via modulating Protein Kinase A and Protein Kinase C signaling. Cell Death and Differentiation 05/2015.
c. Barnea E.R, Almogi-Hazan O, Or R, **Mueller M**, Ria F, Weiss L, Paidas M.J. Immune Regulatory and Neuroprotective Properties of Preimplantation Factor: from Newborn to Adult. Pharmacology and Therapeutics (Accepted for Publication 10/2015)
d. Shainer R, Almogi-Hazan O, Berger A, Hinden L, **Mueller M**, et al. PreImplantation factor (PIF) therapy provides comprehensive protection against radiation induced pathologies. Oncotarget. 2016 Jul 16

5. Non-coding RNAs

Non-coding ncRNAs are broadly classified as microRNAs (miRNA, <200 nucleotides) or long ncRNAs (lncRNA, >200 nucleotides). ncRNAs are not only transcriptional noise as previously suggested but hold specific functions. Both miRNAs and lncRNAs are important regulators of physiological and pathological responses in cancer and inflammation associated diseases. In particular, lncRNA H19 is essential for human tumor growth and with increased expression in cancer tissues. Given that endometriosis affects approximately 15% of reproductive aged women and is associated with chronic pelvic pain and infertility, we hypothesized that H19 may contribute to endometriosis as well. We reported that H19 expression is significantly decreased in the eutopic endometrium of women with endometriosis as compared to normal controls. We show that decreased H19 increases let-7 activity, which in turn inhibits Igf1r expression at the post-transcriptional level, thereby contributing to reduced proliferation of endometrial stromal cells. We propose that perturbation of this newly identified H19/Let-7/IGF1R regulatory pathway may contribute to impaired endometrial preparation and receptivity for pregnancy in women with endometriosis.

We assessed H19 function in type 2 diabetes as well. We reported that H19 is significantly decreased in muscle of human subjects with type-2 diabetes and insulin resistant rodents. This decrease leads to increased bioavailability of let-7, causing diminished expression of let-7 targets, which is recapitulated in vitro where H19 depletion results in impaired insulin signaling and decreased glucose uptake. Furthermore, acute hyperinsulinemia downregulates H19, a phenomenon that occurs through PI3K/AKT-dependent phosphorylation of the miRNA processing factor KSRP, which promotes biogenesis of let-7 and its mediated H19 destabilization. We recently report that the H19 binds to and inhibits S-adenosylhomocysteine hydrolase (SAHH), the only mammalian enzyme capable of hydrolyzing S-adenosylhomocysteine (SAH). SAH is a potent feedback inhibitor of S-adenosylmethionine (SAM)-dependent methyltransferases that methylate diverse cellular components, including DNA, RNA, proteins, lipids, and neurotransmitters. Our results uncover an unanticipated regulatory circuit involving broad epigenetic alterations by a single abundantly expressed lncRNA that may underlie gene methylation dynamics of development and diseases and suggest that this mode of regulation may extend to other cellular components.

a. Gao Y, Wu F, Zhou J, Yan L, Jurczak M, Lee H, Yang L, **Mueller M,** Zhou X, Dandolo L, Szendroedi J, Roden M, Flannery C, Taylor H, Carmichael G, Schulman G, Huang Y (2014). The H19/let-7 double-negative feedback loop contributes to glucose regulation in muscle cells. Nucleic Acids Res. 2014 Nov 15.
b. Ghazal S, McKinnon B, Zhou J, **Mueller M,** Yang L, Mueller M, Flannery C, Huang Y, Taylor H (2014). H19 lncRNA alters stromal cell growth via IGF signaling in the endometrium of women with endometriosis. (EMBO Mol Med. 5/2015).
c. Zhou J, Yang L, Zhong T, **Mueller M**, Men Y, Zhang N, Xie J, Giang K, Chung H, Sun X, Lu L, Carmichael G, Taylor H & Huang Y. H19 lncRNA alters DNA methylation genome-wide by regulating S-adenosylhomocysteine hydrolase. Nature Communications 12/2015

My full bibliography is available at:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1xquufpni5Qv/bibliography/48331993/public/?sort=date&direction=ascending.

D. Research Support ongoing and completed

a. NIH/NIAID STTR 1R41AI120546-01. Paidas (PI). 07/2015-06/2017. Treatment of Acute Radiation Syndrome using PIF, a Natural Immune Modulator. Role: Co-Investigator.
b. NIH STTR Phase I GRANT 11806658. Paidas (PI). 01/2017-12/2017 PreImplantation Factor plus hypothermia to treat neonatal brain injury. Role: Co-Investigator
c. Cryo-Save/Esperite. Surbek (PI). 06/2015-05/2017. Neurogenic potential of umbilical cord-derrived mesenchymal stem cells. Role: Co-Investigator
d. University of Bern. Mueller (PI). 03/2015-02-2017. WJ-MSCs and sPIF as therapeutic options for perinatal brain injury. Role: Principal-Investigator
e. NIH/NICHD 1R41HD085744-01A1 Paidas (PI). 12/2016-06/2018. Preimplantation Factor plus hypothermia to treat neonatal brain injury. Role: Co-Investigator
f. Ruth & Arthur Scherbarth Stiftung Bern. Surbek (PI). 2012-2013. Stem Cell Transplantation for the neuroregeneration in a rat preterm neonatal brain injury model. Role: Co-Investigator