

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME: **Detlef Obal, MD, PhD, DESA**

eRA COMMONS USER NAME (credential, e.g., agency login): d0obal01

POSITION TITLE: **Assistant Professor**

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

INSTITUTION AND LOCATION	DEGREE (if applicable)	MM/YY	FIELD OF STUDY
University of Düsseldorf, Germany, University of Manchester, UK	MD	06/1999	General Medicine
University of Düsseldorf, Germany Board Certification – Germany European Diploma of Anesthesiology Fellowship	board certified DESA	09/2004 10/2005 2004-2005	Anesthesiology Anesthesiology Neuroanesthesia/ Critical Care
University of Louisville, KY, USA	PhD	2014	Physiology and Biophysics
Cardiovascular Institute, Stanford University, USA	Postdoctoral	2018	Personalized Medicine in CV Anesthesiology

A. PERSONAL STATEMENT

I started my basic research career as a medical student and trainee in the Department of Heart and Circulation Physiology (Head: Professor J. Schrader, supervision: Professor W. Schlack/ V.Thämer), University of Düsseldorf, Germany, focusing on the effect of **anesthetic preconditioning and cardiac protection**. These studies were primarily focused on cardiac physiology and mechanics and I received my MD degree for the thesis “Effect of acidotic blood reperfusion on reperfusion injury after coronary artery occlusion in the dog heart.” Envisioning my future career in basic science, I decided to move to the US to receive further training in molecular biology/ cardiology at the *Institute of Molecular Cardiology (IMC)* at the University of Louisville. I enrolled in the PhD program of the Department of Physiology and Biophysics and worked with Gregg Rokosh, PhD, under the supervision of Dr. Roberto Bolli, on the effect of **stromal-derived factor 1 α (SDF) on cardiac regeneration**. After completion of my PhD thesis, I continued my postdoctoral work under the supervision of Aruni Bhatnagar, PhD with the focus on cardio-vascular effects of diabetic metabolic changes on vascular and cardiac function at the *Diabetes and Obesity Center (DOC)* of the University of Louisville. Subsequently, I worked on anesthetic induced vascular dysfunction caused by TRPA1 channel activation. Unfortunately, despite receiving a seed grant from the University, my clinical duties increased making bench-based research impossible. Following my desire to pursue a career in basic science, I moved to Stanford to work in Dr. Joseph Wu’s lab. **With now 80% research time, I started to study the effect of anesthetics, in particular chronic opioid administration, on cardiovascular function in different genetic models using human induced pluripotent stem cells.**

B. POSITIONS AND HONORS**Positions and Employment**

1999-2004	Internship and Residency in Anesthesiology and Intensive Care (Mentor: J. Tarnow, MD, PhD)
2004-2005	Neuroanesthesia Fellowship, University of Düsseldorf, Germany
2005-2006	Staff Anesthesiologist, University of Düsseldorf, Germany
2005	Diplomate of the European Society of Anesthesiology (DESA)
2006-2018	Assistant Professor, Department of Anesthesiology, University of Louisville, KY
2006-2018	Postdoctoral scientist, IMC and DOC, University of Louisville, KY
2008-2018	Member Departmental Research Board, Department of Anesthesiology, University of Louisville, KY
2018-	Assistant Professor, Department of Anesthesiology, Perioperative, and Pain Medicine, Stanford University, CA

Other Experience and Professional Memberships

2000-	Member of German Society of Anesthesiology (DGAI)
2003-2011	Member of European Society of Anesthesiology (ESA)
2006-	Member of American Heart Association (AHA), International Anesthesia Research Society (ISAR), American Society of Anesthesiology (ASA), Specialist Register British Medical Council (GMC)
2019-	Member Society for Stem Cell Research (ISSCR)
2013-	Editorial board member: Frontiers in Physiology, Oxidant Physiology, BioMed Research International – Anesthesiology, Anesthesia&Analgesia

Honors

1999	Doctoral Thesis “Magna cum laude” Heart and Circulation Physiology, University of Düsseldorf, Germany
2003	First prize abstract competition Euroanesthesia congress, Glasgow, Scotland
2014	Deans Citation Award, University of Louisville
2018	Stanford University Cardiovascular Institute Seed Grant

C. Contribution to Science

- Cardiovascular Biology:** Expanding on my studies at the University of Duesseldorf, Germany, I used a diversity of knockout and transgenic mouse models to investigate the role of key proteins responsible for myocardial protection through **ischemic preconditioning**. Our initial manuscript describes that nitric oxide plays an important role in mitochondrial transition pore opening during ischemic preconditioning and that nitric oxide’s bioavailability can be significantly increased by overexpressing ecSOD in cardiomyocytes. For the first time, I could demonstrate the crucial interaction of nitric oxide and free oxygen radicals during cardiac protection in isolated mouse cardiomyocytes. Subsequently, we demonstrated that genetic deficiency of another antioxidant enzyme (i.e. glutathione s-transferase pi) diminishes the protection against ischemia reperfusion injury through lack of detoxification of cytotoxic aldehydes, such as acrolein.
 - West MB, et al. Cardiomyocyte-specific expression of inducible nitric oxide synthase protects against ischemia/reperfusion injury by preventing mitochondrial permeability transition. **Circulation** **2008**; Nov 4;118(19):1970-8. *PMCID: PMC2763350*
 - Obal D, et al. Cardiomyocyte-restricted overexpression of extracellular superoxide dismutase increases nitric oxide bioavailability and reduces infarct size after ischemia/reperfusion. **Basic research in cardiology** **2012**;107(6):305. *PMCID: PMC3505528*
 - Conklin DJ, et al. Genetic deficiency of glutathione S-transferase P increases myocardial sensitivity to ischemia-reperfusion injury. **Circ Res** **2015**; 117: 437-49, *PMID: 26169370*
 - Gibb AA, et al. Exercise-Induced Changes in Glucose Metabolism Promote Physiological Cardiac Growth. **Circulation** **2017** Nov 28;136(22):2144-2157. *PMID: 28860122*
- Cardiac regeneration/ development:** The importance of the chemokine CXCL12 (SDF1 α) and its receptor CXCR4 in cardiac regeneration was unknown. Using a transgenic mouse model overexpressing **SDF1 α** within cardiomyocytes allows us to identify a novel mechanism promoting cardiomyocyte regeneration. We identified casein kinase 1 α as a significant mediator of SDF1 α -induced cardiac regeneration. These findings were confirmed by in vivo and in vitro assays suggesting increased cardiomyocyte proliferation after SDF1 α treatment. In addition, we used lentivirus transfer of **casein kinase 1 α** to demonstrate that its overexpression was causal for cardiac proliferation. Our experiments illustrated a close relationship between **chemokines and cardiac regeneration, cardiomyocyte proliferation, and cardiac development**.
 - Obal, D. Myocyte-specific overexpression of stromal cell-derived Factor 1 facilitates cardiac regeneration and improves myocardial function after infarction in mice." (2014). *Electronic Theses and Dissertations*. Paper 1076. <https://doi.org/10.18297/etd/1076>
- As a **clinical-scientist** working as an attending anesthesiologist in operating room and the ICU, I initiated and participated in multiple clinical trials. Trained as a **cardiovascular anesthesiologist**, I am particularly interested in the perioperative care of high-risk cardiac patients undergoing non-cardiac surgery. Nitrous oxide has been used for over 150 years in anesthesia, but it was unclear whether it would be safe to use in

patients with coronary artery disease. Therefore, I was excited to be part of the largest multicenter trial investigating the effect of nitrous oxide on perioperative morbidity and mortality in high-risk patients undergoing non-cardiac surgery (**ENIGMA II trial**). In a series of publications, we demonstrated that the administration of nitrous oxide is safe and does not increase the risk for myocardial infarction after non-cardiac surgery.

At the time of polypharmacy and personalized medicine, it was concerning that a well known QTc prolonging anti-emetic (i.e., ondansetron) was given almost unrestricted to many patients perioperatively. This rised the question, whether adding ondansetron to the mixture of already known **QTc prolonging perioperative** medications (i.e., opiates, hypnotics and others) would cause any harm to patients. Interestingly, in a retrospective analysis of more than 2500 patients, we did not find any increase risk of **cardiac arrhythmias** after administration of ondansetron and concluded that there would be no increased risk using ondansetron in the perioperative setting. This study was critical in developing my interest in **personalized medicine** and using **human inducible pluripotent stem cells** to individualize patients' anesthesia and critical care.

- 3.1. Myles PS, et al. The safety of addition of nitrous oxide to general anaesthesia in at-risk patients having major non-cardiac surgery (ENIGMA-II): a randomized, single-blind trial. **Lancet** **2014**; 384: 1446-54 *PMID: 25142708*
- 3.2. **Obal D**, et al. Perioperative doses of ondansetron or dolasetron do not lengthen the QT interval. **Mayo Clin Proc** **2014**; 89 (1): 69-80 *PMID: 24388024*
- 3.3. Beattie WS, et al. Implication of Major Adverse Postoperative Events and Myocardial Injury on Disability and Survival: A Planned Subanalysis of the ENIGMA-II Trial. **Anesth Analg.** **2018** Mar 12. *PMID: 29533264*
- 3.4. Corcoran T, et al. Intraoperative dexamethasone does not increase the risk of postoperative wound infection: a propensity score-matched post hoc analysis of the ENIGMA-II trial (EnDEX). **Br J Anaesth.** **2017** Feb;118(2):190-199. *PMID: 28100522*
- 3.5. Kim R, et al. Perioperative analgesic administration during the 2018 parenteral opioid shortage in the United States - A retrospective analysis. *Journal of Clinical Anesthesia* 2020; *PMID: 109892*

Complete list of 41 publications at <https://profiles.stanford.edu/detlef-obal?tab=publications>

D. Additional Information: Research Support and/or Scholastic Performance

Current Research Support

7/1/19-6/30/21 Stanford Maternal & Child Health Research Institute
Transdisciplinary Initiatives Program (TIP) Award
Role: Principal investigator

Past Research Support

4/1/2017-3/30/2019 Funder: University of Louisville
Basic Science Research Award
Role: Principal investigator

1/2009-1/2014 Funder: Canadian Research Foundation
Nitrous Oxide Anesthesia And Cardiac Morbidity – Enigma Ii Trial (PI: Paul Myles)
Multicenter clinical trial investigating the effect of nitrous oxide anesthesia on cardiac morbidity in high-risk patients undergoing non-cardiac surgery.
Role: Principal investigator Louisville recruiting side.

3/2017-8/2018 Funder: NIH 5R01HL122581-03
Cardiac Pathophysiology Of Histidyl Dipeptides
Role: Co-Investigator/ Collaborator (PI: Shahid Baba)

9/2008-8/2018 Funder: NIGMS 5P20GM103492-10
Center For Excellence In Diabetes And Obesity Research
The specific objective of the Center is to develop a basic and clinical understanding of the molecular mechanisms of diabetes and obesity and how they contribute to the burden of cardiovascular disease. In this focus I am studying the impact of hyperglycemia on cardiac

reparative potential by mesenchymal and cardiac specific stem cells and whether modulation of cardiac environment increases regeneration tendency in diabetes.

Role: Collaborative Scientist (PI: Aruni Bhatnagar, PhD)

Scholastic Performance

- 2006- **Reviewer:** for British Journal of Anesthesiology, American Journal of Cardiology, Cardiovascular Diabetology, Journal of Cellular and Molecular Neurobiology, Toxicology and Applied Pharmacology, Critical Care, Journal of Clinical Psychopharmacology, BMC Anesthesiology
- 2007-2014 **Local PI of the multicenter ENIGMA II trial** (36 centers) investigating the effect of nitrous oxide in high risk cardiovascular patients undergo non-cardiac surgery.
- 2011- **Annual abstract reviewer at the AHA Scientific Sessions:** Basic science abstracts “Ischemia Reperfusion Injury” section; Basic science abstracts “Cardiac regeneration/ cell therapy - Experimental” section
- 2018- **Assistant Editor:** Anesthesia&Analgesia