Oxidative stress, i.e. an increase in reactive oxygen species formation or imbalance with their formation and metabolism, is a hallmark of many cardiovascular and other diseases. In fact, there is hardly any disease where oxidative stress has not been suggested at one point of time to play a role as a pathomechanism. Yet after decades of research there is no therapeutic in the clinic that is based on an antioxidant mechanism. In fact, the non-targeted preventive application of vitamins and other supposedly antioxidant substances is associated with higher mortality. Is the oxidative stress theory wrong?

Probably not, but it needs a major amendment and an entirely different approach to exploiting it therapeutically. Data will be presented on delineating oxidative stress as a signalling network of ROS generators, ROS targets and ROS metabolisers, some of which inactivate, other toxify ROS. Each of these may play a specific role, or no role, in a given disease state. Identifying these pathomechanism will lead and has led to specific targets and highly specific therapies. Importantly these will leave essential physiological functions of ROS untouched. Targets and the ROS-relevant pathway also extends to NO-cGMP signalling. This entire network is clinically relevant and will open a new chapter of Radical Medicine.

Finally, when validating different indications, we came across non-expected disease states, which confused us as we set out working with what we thought were cardiovascular targets. However, the ROS-cGMP network is relevant to diverse disease phenotypes such diabetic end-organ damage, asthma, stroke, Alzheimer’s disease, and pulmonary hypertension etc. This all made sense when we came across Barabasi’s diseasome, the network of human diseases. All of these phenotypes clustered in one subnetwork. These clusters are likely formed by common mechanisms. Thus the ROS-cGMP network seems to define this cluster. Thus disease should no longer be defined by organs, symptoms or the first doctor who described the symptoms, but only by the molecular pathomechanism.

Fully validating this and expanding it to other clusters of the diseasome will introduce a Radically New Medicine, a Medicine that is fully digitalised and based on big data, Medicine 4.0. We are beginning to take first looks into this exciting future.
**Executive Statement**

Harald Schmidt is Professor & Chair of Pharmacology & Personalised Medicine at the Cardiovascular Research Institute Maastricht, co-leader of Maastricht University’s Faculty of Health, Medicine and Life Sciences innovation platform, and Board Member of the Maastricht Institute of Advanced Studies at Maastricht University, Netherlands. He leads a research program as European Research Council Advanced Investigator, a EUROSTAR programme, and founded a European Science Foundation COST Action. Before he had worked in Australia, Germany and USA in different academic and business leadership positions. These include chair of Monash University’s Centre for Vascular Health, Australia, different chairs in pharmacology and director of a drug discovery CRO at TransMIT, Giessen, Germany. He also co-founded and for two years led as CEO Vasopharm GmbH, a drug discovery company now entering into phase III clinical development. His research focuses on cardiovascular and neurological disease mechanisms, target validation, drug and biomarker discovery, personalised and network medicine. Professor Schmidt has published over 160 peer-reviewed papers, reviews, books and patents (Hirsch-index of 75, m=2.6; Google-Scholar: tinyurl.com/q4july7). He is a member of the European Society of Cardiology Working Group - Cardiovascular Pharmacology and Drug Therapy, Section Editor of the Public Library of Science. He has been awarded the Roche Molecular Biochemicals Research Prize for Cell Biology, the Phoenix Research Prize in Pharmacy, and the Pro Scientia Prize.

**Professional appointments**

2010- Professor of Pharmacology and Personalised Medicine, Maastricht University, The Netherlands

2009 Associate Dean International Research, Faculty of Medicine, Nursing and Health Sciences

2007-2009 Director, Centre for Vascular Health, Monash University, Australia

2005-2009 Professor and Head, Department or Pharmacology, Monash University, Australia

2000-2005 Professor and Head of the Rudolf-Buchheim-Institute for Pharmacology, Justus-Liebig-University, Gießen, Germany

1996-1999 Professor of Pharmacology and Toxicology, University of Würzburg, Germany

CEO of Vasopharm GmbH, Würzburg, Germany

1992-1996 Principal Research Fellow equivalent, Department of Medicine, Clinical Research Group, University Clinics, Würzburg, Germany

1990-1992 Adjunct Assistant Professor, Northwestern University Medical School, Department of Pharmacology, Chicago, USA

Senior Research Scientist, Abbott Laboratories, North Chicago, USA

1989-1990 German Research Council (DFG)-Postdoctoral-Fellow, Northwestern University Medical School, Department of Pharmacology, Chicago, USA

1987-1989 German Research Council (DFG) Postdoctoral Fellow, Free University Berlin, Institute of Pharmacology, West-Berlin, Germany
1986 Karl-Duisberg-Fellowship, Royal Melbourne Hospital, Department of Clinical Pharmacology, University of Melbourne, Australia

Clinical experience

- 2007-2009: Clinical Pharmacologist in Southern Health Hospital, Vascular Medicine Outpatient Clinic
- 2006: Southern Health Therapeutics and Adverse Drug Reactions Committees
- 2004: Successful market launch of a clinical cardiovascular therapeutic monitoring kit
- 2007: One drug candidate (NOS inhibitor) entered clinical development
- 2006: Honorary Appointment at Monash Medical Centre
- 2000-2005: Ethics Committees (University Clinics, Gießen)
- 1999-2000: Clinical Pharmacology activity, participation in Quality Use of Medicine Committee (University Clinics, Würzburg and Gießen), Therapeutics Committee (Southern Health, Melbourne); ward rounds; Chair of Natural Compounds Forum (2001-2005, Germany)
- 1999, 2006: Active member of German and Australian Cardiology Societies
- 1989: Active member of German Society for Clinical Pharmacology

Main clinical interests

1987-: Pharmacology, Hypertension, PAD, Stroke
2000-: ongoing: Clinical trial design and assessment
2007-: ongoing: Personalized medicine

Teaching experience

1987-1989: Pharmacology for Medical Students, University of Berlin
1992-2000: Pharmacology for Medical, Pharmacy Students, University of Würzburg
2000-2005: Pharmacology for Medical, Dentistry and Science Students
2006-ongoing: Editor of a leading German Pharmacology text book (Estler-Schmidt)
2007-2009: Monash University, Medicine, Medical Course Management Committee
2010-: Curriculum committees, Faculty of Medicine and Life Sciences; Honours students committee

Management positions

- Professor of Pharmacology for Pharmacists, Würzburg (1996-2000)
- Member University Council, Würzburg (1996-1998)
- Head of Department of Pharmacology and Toxicology, Gießen (2000-2005)
- Member of Faculty Academic Board, Gießen, Germany (2002-2005)
- Director University Animal Facility, Gießen (2003-2005)
- Member of University Ethics Committee, Gießen, Germany (2002-2004)
- Director of Centre for Vascular Health, Melbourne (2006-2009)
Main research themes

1. Molecular Pharmacology
2. Chemical Biology
3. Drug Discovery
4. Personalized/individualized medicine

List of publications (H-index 75; m=2.7)

Wi-1: Scientific publication in international journal mentioned in the Social Science Citation Index, Science Citation Index or Arts & Humanities Citation Index with Impact Factor


synthesis in endothelial cells and N1E-115 neuroblastoma cells Eur J Pharmacol 183: 1625-1626 “IF=2.432” (13)


histochemistry, NOS histochemistry, and colocalization with GABA Neurosci Lett 157, 157-161 “IF=2019” (153)


37. Schilling K, Schmidt HHHW and Baader SL (1994) Nitric oxide synthase expression reveals compartments of cerebellar granule cells and suggests a role for mossy fibers in their development Neuroscience 59: 893-903 “IF=3456” (60)


44. Kharazia VN, Schmidt HHHW, Weinberg RJ (1994) Type I nitric oxide synthase fully accounts for NADPH-diaphorase in rat striatum, but not cortex Neuroscience 62: 983-987 “IF=3456” (72)


Pfleiderer W, Schmidt HHHW (1998) Anti-pterins as tools to characterize the function tetrahydrobiopterin in NO synthase J Biol Chem 273, 33142-33149 “IF=25854” (30)


Ser239 as in vivo marker of endothelial function Mol Pharmacol 61, 312-319 “IF=4612” (10)


100. Reif A, Shutenko Z, Schmidt HHHW (2004) Superoxide dismutase and catalase are required to detect NO from both coupled and uncoupled neuronal NO synthase Free Rad Biol Med 37:988-997 “IF=4971” (1)


116. Miller AA, Drummond GR, Mast AE, BSc, Schmidt HHHW, Sobey CG (2007) Effect of Gender on NADPH-Oxidase Activity, Expression and Function in the Cerebral Circulation: Role of Estrogen. Stroke 38:2142-2149 “IF=5.855” (n/a)


