Inflammation: purinergic signaling and early detection by 19F- MRI

Prof. Jürgen Schrader,

Institute of Molecular Cardiology, University of Düsseldorf, Germany

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Inflammation is a hallmark of many of the major diseases, such as autoimmune diseases, neurological disorders, myocardial infarction, transplant rejection and cancer. Pharmacologic inhibition of the inflammatory response can therefore favorably influence disease progression. However, new anti-inflammatory drugs and measuring the effectiveness of treatment inflammatory burden - by in vivo imaging technologies is still a challenging issue.

This seminar I will discuss two main issues:

Role of extracellular adenosine formed by CD73 on immune cells and the anti-inflammatory action of adenosine A2A receptors. We have shown that loss of CD73 results in a proinflam-matory phenotype 1, 2 and prolongs the healing process after myocardial infarction3, 4. Phos-phorylated A2A agonists serve as novel prodrug for local anti-inflammatory drug delivery devoid of vasodilatory side effects 5.

We have developed a sensitive MRI method which permits tracking of circulation monocytes/macrophages previous labeled by intravenous injection perfluorcarbon (PFC) containing nanoparticles (130 nm) 6. PFC -labeled monocytes/macrophages accumulate at the site of inflammation and can be measured by 19F-MRI as "hot spot" in disease states such as trans-plant rejection7 and myocarditis8. 19F-MRI is a background free technique and PFC has been already in the clinic as blood substitute. Recent experiments on the translation of 19F-MRI from mice to pigs in a clinical scanner at 3T will be discussed. 1. Koszalka, P. *et al.* Targeted disruption of cd73/ecto-5'nucleotidase alters thromboregulation and augments vascular inflammatory response. *Circ. Res.* **95**, 814-821 (2004).

2. Zernecke, A. *et al.* CD73/Ecto-5 '-nucleotidase protects against vascular inflammation and neointima formation. *Circulation* **113**, 2120-2127 (2006).

3. Bonner, F., Borg, N., Burghoff, S., & Schrader, J. Resident cardiac immune cells and expression of the ectonucleotidase

enzymes CD39 and CD73 after ischemic injury. *PLoS. One.* **7**, e34730 (2012).

 Bonner, F. *et al.* Ecto-5'-nucleotidase on immune cells protects from adverse cardiac remodeling. *Circ. Res.* **113**, 301-312 (2013).
Floegel, U. *et al.* Selective activation of adenosine A2A receptors on immune cells by a CD73 dependent prodrug suppresses joint inflammation in experimental rheumatoid arthritis. *Science Translational Medicine*(2012).
Flogel, U. *et al.* In vivo monitoring of inflammation after cardiac and cerebral ischemia by fluorine magnetic resonance imaging. *Circulation* **118**, 140-148 (2008).

7. Flogel, U. *et al.* Noninvasive Detection of Graft Rejection by In Vivo 19F MRI in the Early Stage. *American Journal of Transplantation* **11**, 235-244 (2011).

8. Jacoby, C. *et al.* Visualization of immune cell infiltration in experimental viral myocarditis by F MRI in vivo. *MAGMA*. (2013).

Curriculum Vitae: Prof. Dr. Jürgen Schrader

Name/position:

Jürgen Schrader, Dr. med. Professor of Physiology Department of Molecular Cardiology, Heinrich-Heine-University Düsseldorf

Family status: born 09.10.1942 in Komotau, Czech Republic, married, three children

Education and Training:

- 1963 1968 Study of Medicine at the Universities of Cologne, Munich and Freiburg. Graduation from Medical School in Freiburg, Germany
- 1967 1969 MD thesis, Department of Physiology, University of Freiburg, (supervisor: Prof. A. Fleckenstein)
- 1968 1970 Internship at the University Hospital Cologne, Germany Academic Positions
- 1970 1971 Fulbright-Hays Scholar at the Department of Physiology, University of Virginia, Charlottesville/USA (supervisor: Dr. R.M. Berne)
- 1971 1974 Research Assistant at the Department of Physiology, University Aachen (RWTH), with Professor Dr. E. Gerlach
- 1974 1980 Research Assistant at the Department of Physiology, University of Munich, Germany
- 1978 Habilitation in Physiology, Munich
- 1980 1983 Associate Professor of Physiology, Department of Physiology, University of Munich, Germany
- 1983 2011 Professor and Head of the Department of Physiology, University of Dusseldorf, Germany
- Since 2011 Research Professor and Head of the Department of Cardiovascular Cardiology (no teaching obligations in the medical curriculum)

Selected Professional Research Duties:

- 1990 1993 Head of the Search Committee for all Associate and Full Professorships in the Basic Sciences at the Charité, Humboldt-University, Berlin, Germany
- 1992 present Visiting Fellow at the Cardiovascular Research Center, University of Virginia, USA
- 1992 1993 President of the German Physiological Society
- 1994 1995 CEO of the start-up "Cardion AG"
- 1995 2001 Head of the Scientific Advisory Board of "Cardion AG"

- 1999 2000 President of the German Society of Cardiology
- 2003 2008 Vice-President for Research and Transfer of Technology at the Heinrich-Heine-University of Dusseldorf, Germany
- 2004 2008 Member of the DFG peer review panel on "Heart and Circulatory System"
- 2002 2012 Founding Chairman and Speaker of the Collaborative Research Centre (SFB 612) on "Molecular analysis of cardiovascular function and dysfunction"

2009 - present Member of the scientific advisory board "Center of Cardiovascular Excellence", Oxford, Great Britain

Sabattical leave:

- 1982 with Martin Rodbell and Constantin Londos, NIDDK, NIH Bethesda, USA, on adenosine signaling.
- 1989 with Sir George Radda, Department of Biochemistry, NMR-Laboratory, University of Oxford, U.K. on MRS/MRI. Own MR-instrument in Duesseldorf in 1990.
- 2003 with Donald Hunt, Department of Chemistry, Laboratory of Biological Mass Spectrometry, University of Virginia, Charlottesville, USA. Own MS-instrument in Duesseldorf in 2004.

Awards and Honors:

- 1994 "Paul-Morawitz" price for research achievements by the German Society of Cardiology
- 1994 Honorary Member of the Humboldt-University, Berlin
- 2006 Member of the "German National Academy of Sciences, Leopoldina"
- 2007 Member of the National Academy of Spain "Real Academia Nacional de Farmacia", Madrid, Spain

Reviewer for funding agencies, including DFG (D), BMBF (D), Wellcome Trust (UK), NSF (USA), NIH (USA), United States - Israel Binational Science Foundation (BSF)

Reviewer for journals, including PNAS, Circ.Res., Circulation, J.Exp.Med., FASEB, PLOS-Biology, AJP, Biophys. J., J. Biol.Chem.

Five most important Publications:

1. Kelm, M., J. Schrader: Control of coronary vascular tone by nitric oxide. Circ. Res.

66:1561-1575, 1990

2. Gödecke, A., U. Flögel, K. Zanger, Z. Ding, J. Hirchenhain, U.K.M. Decking and

J. Schrader: Disruption of myoglobin in mice induces multiple compensatory mechanisms. Proc. Natl. Acad. Sci. USA 96(18): 10495-10500, 1999

3. Flögel, U., M.W. Merx , A. Gödecke, U.K.M. Decking, and J. Schrader:

Myoglobin: a scavenger of bioactive NO. Proc.Natl.Acad.Sci.USA 98(2): 735-740, 2001 4. Koszalka, P., B. Özüyaman, Y. Huo, A. Zernecke, U. Flögel, N. Braun, A. Buchheiser,

U.K.M. Decking, M.L. Smith, J. Sévigny, A. Gear, A.-A. Weber, A. Molojavyi, Z. Ding, C. Weber, K. Ley, H. Zimmermann, A. Gödecke and J. Schrader: Targeted disruption of cd73/ecto-5⁻-nucleotidase alters thrombo-regulation and augments vascular inflammatory response. Circ.Res. 95(8):814-821, 2004

5. Flögel U, Burghoff S, van Lent PL, Temme S, Galbarz L, Ding Z, El-Tayeb A, Huels S, Bönner F, Borg N, Jacoby C, Müller CE, van den Berg WB, Schrader J. Selective Activation of Adenosine A2A Receptors on Immune Cells by a CD73-Dependent Prodrug Suppresses Joint Inflammation in Experimental Rheumatoid Arthritis. Sci. Transl. Med. 4:146ra108, 2012