CURRICULUM VITAE

PERSONAL INFORMATION

Name	Zeerleder
First name	Sacha Sergio
Date of birth	June 8th, 1970
Nationality	Swiss (Citizen of Bern)
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EDUCATION

07/2019	Venia docendi (PD) and Associate Professor, Medical Faculty, University of Bern
10/2018	Board certificate in Hematology (FMH)
04/2016	Full Professor for translational Immunohematology at the University of Amsterdam, the Netherlands
12/2015	License for academic teaching, University of Amsterdam, the Netherlands
04/2010	Board certificate in Hematology, Dutch Hematology Association (NVH), the Netherlands
09/2007	Board certificate in Internal Medicine, Dutch Association of Internal Medicine, MSRC of the Royal Dutch Medical Association, the Netherlands
05/2007	Board certificate in Internal Medicine (FMH)
02/2007	PhD Thesis, University of Amsterdam, the Netherlands
02/2006	Postgraduate training "Advanced Immunology", University of Amsterdam, the Netherlands
05/1999	Doctoral Thesis in Medicine, University of Bern
12/1998	ECFMG United States Board Certification (Educational Commission for Foreign Medical Graduates (average ranking score >90%)
1991 - 1997	Bachelor and master in Medicine, Faculty of Medicine, University of Bern

EMPLOYMENT HISTORY

08/2018 - present	Physician in Chief, Department of Hematology and Central Hematology Laboratory (UKH-HZL), Inselspital, Bern University Hospital, Switzerland; Director: Prof. A. Angelillo-Scherrer
04/2010 - 07/2018	Senior Attending, Department of Hematology, Academic Medical Center, Amsterdam (Directors: Prof. R. van Oers/Prof. M.J. Kersten) and staff member, Department of Immunopathology, Sanquin, Amsterdam, The Netherlands (Director: Prof. M. van Ham)
10/2008 - 03/2010	Resident, Department of Hematology, Academic Medical Center, Amsterdam, The Netherlands (Prof. R. van Oers)
05/2005 - 09/2008	Post-doctoral fellow, Department of Immunopathology, Sanquin, Amsterdam, The Netherlands (Prof. L. Aarden)
01/2004 - 04/2005	Resident, Department of Hematology and Central Hematology Laboratory (UKH-HZL), University Hospital, Bern, Switzerland (Prof. B. Lämmle)
10/2001 - 12/2003	Resident, Department of Internal Medicine, Hospital Center of Biel, Switzerland (Prof. A. Gerber); Internal fellowships dep. of Emergency and Intensive Care (Dr. C. Jenni) and dep. of Nephrology (Dr. Z. Gluck)
02/2001 - 09/2001	Resident, Department of Hematology and Central Hematology Laboratory (UKH-HZL), Inselspital, Bern (Prof. B. Lämmle)
01/1999 - 01/2001	Research Fellow, Department of Hematology and Central Hematology Laboratory (UKH-HZL), Inselspital, Bern (Prof. B. Laemmle/Prof. Dr. W. A. Wuillemin) and Sanquin, Amsterdam, The Netherlands (Prof. E. Hack)
01/1998 - 12/1998	Resident, Department of Internal Medicine, Hospital of Fraubrunnen, Jegenstorf, Switzerland (Dr. H. Marty)

INSTITUTIONAL RESPONSIBILITIES

08/2018 - present	Director Transfusion Medicine, Hemovigilance and Laboratory of Stem Cell Therapy
08/2018 - present	Director stem cell transplantation program (including JACI), University Hospital Bern
08/2018 - present	Vice-director, Center for Hematoncology, University Cancer Center Inselspital (UCI)
08/2018 - present	Principle investigator, Department for BioMedical Research, University of Bern, Switzerland
03/2010 - present	Principle investigator, Department of Immunoppathology, Sanquin Research, Amsterdam, The Netherlands

03/2010 - 07/2018	Senior Consultant Hematology (Academic Medical Center and referring non-academic hospitals North Holland), Head Transfusion Laboratory and Special hematology Laboratory, Academic Medical Center, Amsterdam, the Netherlands
03/2010 – 03/2014	Deputy Director of the Cellular Program (autologous and allogeneic stem cell transplantation)
04/2014 – 07/2018	Director of the Cellular Program (autologous and allogeneic stem cell transplantation, CAR-T cells)
03/2010 - 07/2018	Principle investigator, Department of Hematology, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

MAIN RESEARCH TOPICS

- Cell-free DNA and DNA-binding proteins in (immune) cytopenia's, graft-vs-host disease and sepsis
- Hemoproteins and systemic inflammation in hemolytic diseases, graft-vs-host disease and sepsis
- Innate immunity and immune reconstitution after hematopoietic stem cell transplantation

MAJOR SCIENTIFIC ACHIEVEMENTS

Since more than 20 years my research is dedicated to the role of innate immunity in human disease, with a special interest in damage-associated molecular patterns (DAMPs) and complement. In the recent years I focused on innate immunity in hematological diseases, including hemolytic diseases (sickle cell disease, paroxysmal nocturnal hemoglobinuria (PNH), thrombotic microangiopathy (TMA), autoimmune hemolytic anemia (AIHA)), Graft-vs-host disease, hematopoietic and immune reconstitution after stem cell transplantation (allogeneic and autologous) as well as conditions defined by systemic inflammation (e.g. sepsis). My approach to study the role of innate immunity in hematological diseases is mainly **TRANSLATIONAL** including basic research, preclinical models and clinical research.

I extensively studied the role of DAMPs in human disease. In 2003 together with Prof. Eric Hack (Sanquin Research, Amsterdam) we were among the first to describe cell-free DNA in the form of nucleosomes - a classical DAMP- to be released from dead cells in sepsis patients and that this cell-free DNA is an reliable marker for severity of inflammation and outcome (1). In addition, we demonstrated that the release of DAMPs, such as cell-free DNA, from dead cell is induced by plasma proteases, such as factor VII-activating protease (FSAP) (2, 3). We demonstrated that FSAP after activation upon contact with structures of dead cells, e.g. histones, induces DNA release and that this process is tightly regulated by plasma serine proteases, such as C1-inhibitor and alpha2-antiplasmin, and Kunitz-like inhibitors, such as tissue-factor pathway inhibitor (TFPI) (2-6). We identified the specific structures of TFPI involved in FSAP inhibition (5). We also demonstrated the proinflammatory effects of cell-free DNA and DNA-binding proteins and identified FSAP as an efficient neutralizer of cytotoxicity of DNA-binding proteins, such as histones (6, 7). We found that cell-free DNA and DNA-binding protein seem to play a crucial role in the pathogenesis of systemic inflammation (e.g. sepsis, GvHD) and that therapeutic neutralization of DAMPs may attenuate inflammation and improve outcome in these clinical situations (8). To date we investigate the efficacy of plasma-purified or recombinant FSAP for therapeutic application to neutralize the harmful effects of DAMPs released during systemic inflammation.
The recent years the mechanism red blood cell (RBC) membrane disintegration with subsequent release of DAMPs (e.g. cell-free hemoglobin and heme) caught my attention. We demonstrated that in more than 50% of the AIHA patients complement activation contributes to RBC destruction, which enables us to test the efficacy of complement inhibitors to halt and prevent RBC lysis in these AHIA patients. The first studies in these patients are promising (9, 10). Interestingly we observed neutrophil activation AHIA patients with complement-mediated RBC destruction (manuscript in preparation). In sickle cell disease, another hemolytic disease, we found neutrophil activation in the form of neutrophil extracellular traps to significantly contribute to organ dysfunction (11). In ongoing studies using patient samples and animal models we try to identify the inflammatory effects of DAMPs released upon hemolysis, such as cell-free hemoglobin, cell free heme and iron. Interestingly, there growing evidence that heme is a central DAMP in systemic inflammation also in the absence of hemolysis. Next, we will investigate the efficacy of scavengers for heme and cell free hemoglobin (e.g. hemopexin, haptoglobin, inducible heme oxygenase) in systemic inflammation due to hemolysis and in the absence of hemolysis (e.g. sepsis)

The understanding of the precise mechanism how DAMPs are released, how this process is regulated and what the peripheral effects of DAMPs are in these diseases is a SINE-QUA-NON to design therapeutic strategies to neutralize DAMPs in order to improve morbidity and mortality in these patients. My research significantly contributed and will contribute to understand these mechanisms and to explore the efficacy of therapies neutralizing the harmful effects of DAMPs.

TECHNIQUES ESTABLISHED IN THE ZEERLEDER LAB

- Protein purification
- Expression of recombinant proteins (plasma proteins)
- Generation of monoclonal and polyclonal antibodies
- Different DNA techniques (digital droplet PCR, etc)
- Cell culture systems (cell lines, iPS)
- Activity and Cytotoxicity assays
- Animal Models (rat, mouse)

BIBLIOGRAPHY

1. Zeerleder S, Zwart B, Wuillemin WA, Aarden LA, Groeneveld AB, Caliezi C, van Nieuwenhuijzen AE, van Mierlo GJ, Eerenberg AJ, Lämmle B, Hack CE. 2003. Elevated nucleosome levels in systemic inflammation and sepsis. Crit Care Med 31: 1947-51
2. Zeerleder S, Zwart B, te Velthuis H, Manoe R, Bulder I, Rensink I, Aarden LA. 2007. A plasma nucleosome releasing factor (NRF) with serine protease activity is instrumental in removal of nucleosomes from secondary necrotic cells. FEBS Lett 581: 5382-8
3. Zeerleder S, Zwart B, te Velthuis H, Stephan F, Manoe R, Rensink I, Aarden LA. 2008. Nucleosome-releasing factor: a new role for factor VII-activating protease (FSAP). FASEB J 22: 4077-84
4. Stephan F, Hazelzet JA, Bulder I, Boermeester MA, van Till JO, van der Poll T, Wuillemin WA, Aarden LA, Zeerleder S. 2011. Activation of factor VII-activating protease in human inflammation: a sensor for cell death. Crit Care 15: R110
5. Stephan F, Dienava-Verdoold I, Bulder I, Wouters D, Mast AE, Te Velthuis H, Aarden LA, Zeerleder S. 2012. Tissue factor pathway inhibitor is an inhibitor of factor VII-activating protease. J Thromb Haemost 10: 1165-71
6. Stephan F, Marsman G, Bakker LM, Bulder I, Stavenuiter F, Aarden LA, Zeerleder S. 2014. Cooperation of factor VII-activating protease and serum DNase I in the release of nucleosomes from necrotic cells. Arthritis Rheumatol 66: 686-93
7. Marsman G, von Richthofen H, Bulder I, Lupu F, Hazelzet J, Luken BM, Zeerleder S. 2017. DNA and factor VII-activating protease protect against the cytotoxicity of histones. Blood Adv 1: 2491-502
8. Zeerleder S. 2018. Factor VII-Activating Protease: Hemostatic Protein or Immune Regulator? Semin Thromb Hemost 44: 151-8
9. Meulenbroek EM, de Haas M, Brouwer C, Folman C, Zeerleder SS, Wouters D. 2015. Complement deposition in autoimmune hemolytic anemia is a footprint for difficult-to-detect IgM autoantibodies. Haematologica 100: 1407-14
10. Wouters D, Zeerleder S. 2015. Complement inhibitors to treat IgM-mediated autoimmune hemolysis. Haematologica 100: 1388-95
11. Schimmel M, Nur E, Biemond BJ, van Mierlo GJ, Solati S, Brandjes DP, Otten HM, Schnog JJ, Zeerleder S, Curama Study G. 2013. Nucleosomes and neutrophil activation in sickle cell disease painful crisis. Haematologica 98: 1797-803

Bern, 15th January 2020

Prof. Dr. med. Dr. phil. Sacha Zeerleder