BIOGRAPHICAL SKETCH

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NAME: Christoph Mueller

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POSITION TITLE: Professor

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
University of Bern, Switzerland	BSc.	7/1980	Biology, Microbiology
University of Bern, Switzerland	MSc	12/1981	Bacteriology
University of Bern, Switzerland	PhD	02/1985	Medical Microbiology
University of Bern, Switzerland	Post-doc	07/1985	Immunology
Stanford University School of Medicine, USA	Post-doc	06/1988	Immunology

A. Personal Statement

Dr. Christoph Mueller is an immunologist with a longstanding interest and expertise in the pathogenesis of immune-mediated disorders and pathologies.

A major aspect of our current experimental work focuses on the contribution of Triggering receptor expressed on myeloid cells-1 (TREM1) to the pathogenesis of inflammatory disorders and immunopathologies. Our current work on TREM1-mediated effects and their regulation was triggered by our initial findings that TREM1 is not only involved in the amplification of acute inflammatory processes, but is also instrumental in chronic inflammatory disorders, notably, in inflammatory bowel diseases (IBD), where activation with an agonistic mAb for TREM1 significantly enhanced the secretion of pro-inflammatory mediators in intestinal macrophages isolated from biopsies from patients with active IBD, and conversely, administration of a blocking peptide (LP17) in mice with active colitis attenuated the progression of the disease. TREM1 is also cleaved from the surface of TREM1 positive cells. We developed an ELISA to monitor the appearance of sTREM1 in the serum of controls; patients with IBD in remission, and patients with IBD with active disease. The generation of a Trem1-deficient mouse line in our lab allowed us to define the consequences of *Trem1* gene deficiency on the clearance of pathogens (which is generally not affected), and the development of immunopathologies (which is generally greatly reduced in the absence of TREM1 signaling). On-going work focuses on the regulation TREM1 mediated signaling and its consequences in carcinogenesis (notably, colitis-induced colorectal carcinoma) and atherosclerosis; and on the impact of distinct TREM-1 SNP's (e.g. rs2234237) on risk factors (e.g. altered carotid intima-media thickness for atherosclerosis) and the extent of sTREM1 shedding in controls and patients with atherosclerosis or IBD. This latter part is done in part in collaboration with the Swiss IBD Cohort Study (with currently approx. 2500 IBD patients enrolled) where we are responsible to maintain the biobank.

B. Positions and Honors

Positions

1988-1992 Research Assistant, Department of Pathology, University of Bern, Switzerland
1992-1997 Assistant Professor, Department of Pathology, University of Bern, Switzerland

1994-2007	Acting Head, Division of Clinical and Experimental Immunopathology, University of Bern, Switzerland
1997	Associate Professor, Department of Pathology, University of Bern, Switzerland
2007 - present	Professor of Experimental Pathology; Head, Division of Experimental Pathology, University of Bern
2008 – 2012	Vice Dean of Research, Medical Faculty, University of Bern, Switzerland
2008 – present	Deputy Director, Institute of Pathology, University of Bern, Switzerland
10/2015 -	Visiting Professor of Neurology, Stanford University Medical Center, Stanford, USA

Honors and additional profession-related activities

1993	HOECHST Prize (co-winner) Medical Faculty, University of Vienna, Austria
2001	Honl Family Senior Investigator Research Award (Crohn's and Colitis Foundation of America)
2003-2004	Scientific President, Swiss Society of Pathology
2006	Best wok in preclinical science (Medical Faculty, Univ. of Bern)
2007-2009	*ad hoc* Member of the Research Council of the Swiss National Science Foundation (Division Biology and Medicine)
2005- present	Member Scientific Board (2005-2007): President) Swiss IBD Cohort Study (SIBDCS)
2005 – present	Member Executive Board, Swiss IBD Cohort Study (SIBDCS)
2005 – present	Head, Biobank, Swiss IBD Cohort Study (SIBDCS)
2009 – present	Member Evaluation Committee, "ambizione Programme", Swiss National Science Foundation (Division Biology and Medicine)
Since 2008	Member Research Committee, Medical Faculty, University of Bern (2008-2012: President of the Research Committee)
Since 2009	Member (Treasurer) Committee of the Swiss Society of Allergology and Immunology
Since 2008	Member of the Steering Committee of the Department for Clinical Research, University of Bern (2008-12: President)

C. Contribution to Science

1 Establishment of in situ hybridization of tissue sections using S-35 labeled RNA probes. During my post-doctoral work in the lab of Dr. Irving L Weissman, Dept. of Pathology, Stanford University Medical Center (1985-88), I contributed to the establishment of *in situ* hybridizations of frozen and paraffin embedded tissue sections using radiolabeled RNA probes. Initially, this technology was successfully used to monitor the distribution of activated cytotoxic T cells and NK cells in graft rejection in mice, but also in patient material as a proof of principle that the detection of activated cytotoxic cells can be used as an early histopathological marker for an ongoing (acute) transplant rejection. This method was subsequently also used to define the precise location and the kinetics of their appearance of tumor necrosis factor (TNF) and related cytokine -expressing cells in autoimmune disorders such as insulin-dependent diabetes mellitus and dacryoadenitis in NOD mice, or in infectious diseases (e.g. leprosy, leishmaniasis). These studies were often the initiation of further more mechanistic investigations where a given mediator (e.g. TNF) was blocked by transgenic (over-) expression of a soluble receptor, or the administration of neutralizing antibodies to prove the non-redundant nature of the defined mediators in the disease process.

C. Mueller, H.K. Gershenfeld, C.G. Lobe, C.Y. Okada, R.C. Bleackley, and I.L. Weissman. A high proportion of T lymphocytes that infiltrate H-2 incompatible heart allografts in vivo express genes encoding cytotoxic cell-specific serine proteases, but do not express the MEL-14- defined lymph node homing receptor. J. Exp. Med. 167: 1124-1136, 1988

C.L. Cooper, **C. Mueller**, T.-A. Sinchaisri, C. Pirmez, J. Chan, G. Kaplan, S. M.M. Young, I.L. Weissman, B.R. Bloom, T.H.Rea, and R.L. Modlin. Analysis of naturally occurring delayed-type hypersensitivity reactions in leprosy by in situ hybridization. J. Exp. Med. 169: 1565-1581, 1989

W. Held, H. R MacDonald, I. L. Weissman, M.W. Hess and **C. Mueller**. Genes encoding tumor necrosis factor a and granzyme A are expressed during development of autoimmune diabetes. Proc. Natl. Acad Sci USA 87: 2239, 1990

R. E. Hunger, S. Müller, J. A. Laissue, M.W. Hess, C. Carnaud, **C. Mueller**. Inhibition of submandibular and lacrimal gland infiltration in NOD mice by transgenic expression of soluble TNF receptor p55. J. Clin. Invest. 98: 954- 961; 1996

2. **Recruitment of effector cells of the innate and adaptive immune system to the site of intestinal inflammation in the digestive tract (including IBD; chronic pancreatitis).**
The cloning of an increasing number genes encoding chemotactic cytokines, together with the previous established methods of in situ hybridizations allowed us to elucidate the critical mechanisms involved in the recruitment of inflammatory cells to the site of inflammation, notably in patients with active Crohn's disease, and ulcerative colitis, but also in patients with chronic pancreatitis. These studies were among the first to demonstrate the critical role for the recruitment of neutrophils, and (inflammatory) monocytes/macrophages in the pathogenesis of IBD, and provided evidence for a selective recruitment and activation *in situ* of cytotoxic T cells in chronic pancreatitis.

Mazzucchelli, C. Hauser, K. Zgraggen, H. Wagner, M. Hess, J.A. Laissue, **C. Mueller.** Expression of interleukin 8 gene in inflammatory bowel disease is related to the histological grade of active inflammation. Amer. J. Pathol. 144: 997-1007; 1994.

K. Z'graggen, A. Walz, L. Mazzucchelli, R. M. Strieter and **C. Mueller**. The C-X-C -chemokine ENA-78 is preferentially expressed in intestinal epithelium of patients with inflammatory bowel disease. Gastroenterology 113: 808-816; 1997.

R.E. Hunger, **C. Mueller,** K. Z'graggen, H. Friess, M.W. Büchler. Cytotoxic cells are activated in cellular infiltrates of alcoholic chronic pancreatitis. Gastroenterology 112: 1656-1663; 1997.

Saurer, P. Reber, T. Schaffner, M. W. Büchler, C. Buri, A. Kappeler, A. Walz, H. Friess and **C. Mueller**. Differential Expression of Chemokines in Normal Pancreas and in Chronic Pancreatitis. Gastroenterology 118:356-367; 2000.

3. **Secreted, and transmembrane tumor necrosis factor in inflammatory bowel diseases, infectious diseases and cardiovascular disorders.**
The pleiotropic effects mediated by the tumor necrosis factor (TNF) and the reported differential binding of transmembrane, vs. secreted TNF to the two TNF receptors prompted us to generate a mouse expressing solely a non-cleavable mutant form of TNF (tmTNF mouse). We previously reported that in the CD4 T cell transfer model of colitis in RAG deficient mice TNF is critical for disease induction. Using our tmTNF mouse we demonstrated that colitis is induced even in the absence of secreted TNF. Similarly, tmTNF is capable to mediate protection in a *M. tuberculosis* infection model in mice, while in a mouse model of atherosclerosis (ApoE-/- mouse) both secreted TNF, and tmTNF were required for full induction of atheroma formation. These data are vital for interpreting the results of anti-TNF treatments, where either only secreted TNF (e.g. by etanercept), or both transmembrane, and soluble TNF (e.g. by infliximab) are targeted.

Mueller C, Corazza N, Trachsel-Loseth S, Eugster HP, Buhler-Jungo M, Brunner T, Imboden MA. Noncleavable Transmembrane Mouse Tumor Necrosis Factor-alpha (TNFalpha) Mediates Effects Distinct from Those of Wild-type TNFalpha in Vitro and in Vivo. J Biol Chem. 274: 38112 - 38118; 1999

N. Corazza, S. Eichenberger, HP. Eugster, **C. Mueller**. Non-lymphocyte derived tumor necrosis factor is required for colitis induction in the RAG2-/- mouse upon transfer of CD4+CD45RBhi T cells. J. Exp. Med. 190(10):1479-1492; 1999.

Olleros ML, Guler R, Corazza N, Vesin D, Eugster HP, Marchal G, Chavarot P, **Mueller C,** Garcia I. Transmembrane TNF induces an efficient cell-mediated immunity and resistance to Mycobacterium bovis

bacillus Calmette-Guerin infection in the absence of secreted TNF and lymphotoxin-alpha. J Immunol. 2002 Apr 1;168(7):3394-401

N. Corazza, T. Brunner, C. Buri, S. Rihs, MA. Imboden, I. Seibold, **C. Mueller**. Transmembrane tumor necrosis factor is a potent inducer of colitis. Gastroenterology 127: 816-25; 2004

4. Conventional and unconventional T cell subsets in intestinal tissue homeostasis and inflammation.

The intestinal mucosa, particularly the intraepithelial compartment, harbors a significant portion of so-called unconventional T cells (TCR$\gamma\delta$ T cells, CD8$\alpha\alpha$ TCR$\alpha\beta$ T cells) that are not negatively selected in the thymus. Despite their substantial numbers, very little is known about their functions *in vivo*. Using TCR transgenic mice, we demonstrated that these (autoreactive) CD8$\alpha\alpha$ TCR$\alpha\beta$ IEL do not become pro-inflammatory even when activated with their cognate antigen (lymphotropic choriomeningitis virus (LCMV)-gp33) during an acute infection with LCMV, but maintain their largely immunosuppressive phenotype. Intriguingly, in contrast to their CD8$\alpha\beta$ TCR$\alpha\beta$ counterparts, they do not differentiate into perforin containing, cytotoxic T cells. Ongoing work now revealed that during chronic inflammatory conditions some of the intraepithelial CD8$\alpha\alpha$ TCR$\alpha\beta$ T cells leave their intraepithelial location and, in contrast to the situation under homeostatic conditions or short term activation, may even appear transiently at extraintestinal sites where they acquire a pro-inflammatory phenotype.

Corazza N, Muller S, Brunner T, Kagi D, **Mueller C**. Differential Contribution of Fas- and Perforin-Mediated Mechanisms to the Cell-Mediated Cytotoxic Activity of Naive and In Vivo-Primed Intestinal Intraepithelial Lymphocytes. J Immunol. 164: 398-403; 2000

S. Müller, M. Bühler-Jungo, **C. Mueller**. Intestinal intraepithelial lymphocytes exert potent protective cytotoxic activity during an acute virus infection. J. Immunol 164:1986-94; 2000

L. Saurer, I. Seibold, S. Rihs, C. Vallan, T. Dumrese, **C. Mueller**. Virus-activation of self-specific TCR$\alpha\beta$CD8$\alpha\alpha$ intraepithelial lymphocytes does not abolish their self tolerance in the intestine, J. Immunol 172:4176-83; 2004

5. Triggering receptor expressed on myeloid cells-1: a key amplifier not only of acute, but also chronic inflammatory disorders.

Triggering receptor expressed on myeloid cells-1 was initially cloned and characterized as a DAP-12 associated receptor, expressed on myeloid cell, which amplified acute inflammatory responses by the group of Dr. Marco Colonna. We first investigated the regulation of TREM1 on myeloid cells at the site where highest concentrations of LPS are to be expected even under homeostatic conditions, i.e. in the intestinal lamina propria. Intriguingly, TREM1 was found to be absent on intestinal macrophages, but was strongly expressed on a macrophage subset at affected intestinal sites in patients with active inflammatory bowel diseases. In a mouse model of colitis, blocking TREM1 signaling significantly attenuated colitis even when the blocking peptide was administered when mice showed clinical signs of disease. To further assess the potential of targeting TREM1 in chronic inflammatory disorders, we generated a *Trem1* gene deficient mouse. We just completed a study where ApoE-/- mice, maintained on a high fat, high cholesterol diet showed a highly attenuated course of atherogenesis when they were on a *Trem1* deficient background. Unexpectedly, in these atherosclerosis-prone mice the presence of TREM1 appears to be critical for the local differentiation of vascular wall macrophages into foam cells.

M. Schenk, A. Bouchon, S. Birrer, M. Colonna, **C. Mueller**. Macrophages expressing triggering receptor expressed on myeloid cells (TREM)-1 are underrepresented in human intestine. J. Immunol 174:517; 2005.

M. Schenk, A. Bouchon, F. Seibold, **C. Mueller**. TREM-1 expressing intestinal macrophages crucially amplify chronic inflammation in inflammatory bowel diseases. J. Clin. Invest 117: 3097-10; 2007.

L. Saurer, S. Rihs, M. Birrer, N. Saxer-Seculic, M. Radsak, **C. Mueller** & The Swiss IBD Cohort Study. Elevated levels of Serum-Soluble Triggering Receptor Expressed on Myeloid cells-1 in patients with IBD do not correlate with intestinal TREM-1 mRNA expression and endoscopic disease activity. J. Crohn's Colitis 6:913-23; 2012

B. Weber, S. Schuster, D. Zysset, S. Rihs, N. Dickgreber, Ch. Schürch, C. Riether, M. Siegrist, Ch. Schneider, H. Pawelski, U. Gurzeler, P. Ziltener, V. Genitsch, F. Tacchini-Cottier, A. Ochsenbein, W. Hofstetter, M. Kopf, T. Kaufmann, A. Oxenius, W. Reith, L. Saurer, **Ch. Mueller**. TREM-1 deficiency can attenuate disease severity without affecting pathogen clearance. PLoS Pathogens 2014; Jan;10(1):e1003900

2 List of publications in Google Citation Scholar
https://scholar.google.ch/citations?user=9Zv676gAAAAJ&hl=de.

D. Research Support

Active

Swiss National Science Foundation: Swiss IBD cohort study (Project # 148422)

Swiss National Science Foundation: “Sinergia Project” (other research groups involved (equal contribution): Andrew Macpherson, Bern, Switzerland; Wolf-Dieter Hardt, ETH Zurich, Uwe Sauer, ETH ZH Switzerland). Project # 154414

Swiss National Science Foundation Project grant to C. Mueller: # 138392

Completed Research Support past 3 years

Swiss National Science Foundation: Swiss IBD cohort study (Project # 134274)

Swiss National Science Foundation: “Sinergia Project” (other research groups involved (equal contribution): Andrew Macpherson, Bern, Switzerland; Wolf-Dieter Hardt, ETH Zurich, Daniela Finke, Basel, Switzerland) (Project #136286).

Swiss National Science Foundation Project grant to C. Mueller: Project # 122560

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