BIOGRAPHICAL SKETCH

NAME: Steffen Jung

POSITION TITLE: Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of Cologne, Germany	PhD	01/1993	Immunology
The Hebrew University, Jerusalem, Israel	postdoc	04/1997	Immunology
Skirball Institute, NYU Medical Center, NY, USA	postdoc	05/2002	Immunology

A. Personal Statement

I was born in Homburg/ Saar, Germany. After undergraduate studies at the University of Bonn, I moved to the Institute of Genetics in Cologne. In the Department of Immunology headed by Prof. Klaus Rajewsky, I performed my PhD under the guidance of Prof. Andreas Radbruch. Specifically, I used the then newly developed gene targeting approach to define cis-acting control elements driving non-coding 'sterile' transcripts in immunoglobulin class switch recombination. In 1993, I moved for post-doctoral training to Israel and joined the laboratory of Prof. Yinon Ben-Neriah at the Lautenberg Center (Hebrew University, Jerusalem) studying transcription factors and kinases in T cell signaling. In 1997, I went to New York for a post-doc in the laboratory of Prof. Dan Littman at the Skirball Institute for Molecular Pathogenesis, NYU Medical Center. My studies there focused on the then newly discovered chemokine receptor CX_3CR1 and its membrane-tethered ligand CX_3CL1/ fractalkine. I generated CX_3CR1^{gfp} mice that became as reporter strain instrumental to define murine monocyte subsets and study brain microglia. Furthermore, I developed in collaboration with Prof. Richard Lang at the Skirball Institute a novel diphtheria toxin receptor-based cell ablation strategy and a mouse model that allowed the study of dendritic cells (DC) in their *in vivo* context by their conditional ablation (CD11c-DTR mice). In 2002, I returned to Israel and joined the faculty of the Department of Immunology at the Weizmann Institute, where I received tenure in 2009 and full professorship in 2015. Current work of the Jung lab aims at elucidating *in vivo* aspects of mononuclear phagocytes, including the definition of developmental pathways and differential functions of monocytes, DC and macrophages. Specifically, the team applies intra-vital imaging, conditional cell and gene ablation and precursor graft-mediated reconstitution, combined with advanced genomic analysis to investigate the biology of these cells in physiological context in health and disease. Recent work of the Jung laboratory focuses on the study of monocyte-derived intestinal macrophages, embryonic-derived brain microglia and lymph node DC, as well as the role of macrophages in metabolic disorders.

B. Positions and Honors

Academic Appointments

2002 - 2009	Senior Scientist, Weizmann Institute of Science, Dpt. of Immunology
2009 - 2015	Associate Professor, Weizmann Institute of Science, Dpt. of Immunology
11/ 2015 - present	Full Professor, Weizmann Institute of Science
02/ 2017 - present	Head, Department of Immunology

Awards and Honors

1993 Post-doctoral Fellowship of *European Molecular Biology Organization*
1995 Post-doctoral Fellowship of *MINERVA Society*
1997 Associate of *Howard Hughes Medical Institute*
1999 Special Fellow Award of *Leukemia & Lymphoma Society*
2002 The Yigal Alon Scholarship ("*Milgat Alon*")
2002 Scholar of the *Benoziyo Center for Molecular Medicine*.
2002 Incumbent of the *Pauline Recanati Career Development Chair*

C. Contribution to Science

(1) During my PhD at the University of Cologne, Germany, I showed I was the first to provide direct evidence for the need of so-called 'sterile' transcripts to allow for the recombination of switch regions located upstream of C_H genes. Specifically, I used a Flp/FRT-based strategy to delete the promoter element driving transcription through the murine $S\gamma1$ switch region and showed that the resulting mice had a deficiency in IgG1 production (*Jung et al., 1993*).
During my post-doctoral studies at the Skirball Institute for Molecular Pathogenesis, NYU medical Center, New York, US, I generated two novel mouse models that became critical tools for subsequent studies by myself and many other researchers.
(2) To study the physiological role of the CX_3CR1 chemokine receptor I generated CX_3CR1^{gfp} mice carrying a targeted insertion of a gene encoding green fluorescent protein in the CX_3CR1 locus (Jung et al., 2000). These mice were instrumental for our identification of murine Ly6C+ and Ly6- monocyte subsets (*Geissmann, Jung and Littman, 2003*), a seminal report that triggered subsequent efforts by many colleagues to investigate these intriguing blood cells and their contributions to inflammation and pathologies in the mouse. Moreover, through collaborative work we established the value of CX_3CR1^{gfp} mice for the back then emerging intra-vital imaging community, by demonstrating dynamics of intestinal macrophages (*Niess et al., 2005*) and brain microglia (*Davalos et al., 2005*).
(3) To probe for the role of dendritic cells in the initiation of in vivo T cell responses I employed, together with the group of Richard Lang, a novel conditional cell ablation strategy, that is based on rendering murine cells sensitive to diphtheria toxin (DT) by cell type-restricted expression of a primate DT receptor (DTR). These animals allowed me to corroborate the unrivaled potential of DC for the priming of naive T cells in intact animals, extending the seminal *in vitro* studies by Steinman

and colleagues (*Jung et al., 2002*). CD11c-DTR mice and the DTR approach have become standard tools in modern immunological research.

Major contributions, since the establishment of my independent laboratory at the Weizmann Institute include

(4) Using a combination of cell ablation and adoptive monocyte transfers, we established that splenic classical DC derive from non-monocytic origin (*Varol et al., 2007*). Moreover, in the same study and a follow up (*Varol et al., 2009*), we showed that Ly6C^{+} monocytes are precursors of intestinal macrophages residing in the lamina propria. Combined with the concomitant identification of precursor cells, such as MDPs (*Fogg et al., 2006*), our studies critically contributed to the realization that our current understanding of mononuclear phagocyte development.

(5) Taking advantage of the prominent expression of CX_3CR1 in monocytes and specific macrophage populations, we generated animals that harbor transgenes encoding conditional and inducible Cre recombinases under the CX_3CR1 promoter (*Yona et al., 2013*). CX_3CR1^{cre} and CX_3CR1^{creER} mice allow us and others to study functions of specific tissue macrophages, including intestinal, heart, adipose tissue and brain (*Goldmann et al. 2013; Goldmann et al., 2016; Molawi et al., 2014; Zigmond et al., 2014*; *Wolf, Boura-Halfon et al. 2017*). Moreover, the animals enabled us to show, that most tissue macrophage compartments are established before birth and in the healthy adult organism largely maintained independent from monocyte input (*Yona et al., 2013*). Together with the work of others and our own recent transcriptome and epigenome profiling efforts (*Lavin et al., 2014*), this study contributed to a paradigm shift and a focus on differential functions of monocyte and embryo-derived tissue macrophages in health and pathology *(Amit et al., 2016; Ginhoux and Jung, 2014*).

References

Amit, I., Winter, D.R., and Jung, S. (2016). The role of the local environment and epigenetics in shaping macrophage identity and their effect on tissue homeostasis. Nat Immunol *17*, 18–25.

Davalos, D., Grutzendler, J., Yang, G., Kim, J.V., Zuo, Y., Jung, S., Littman, D.R., Dustin, M.L., and Gan, W.-B. (2005). ATP mediates rapid microglial response to local brain injury in vivo. Nat Neurosci *8*, 752–758.

Fogg, D.K., Sibon, C., Miled, C., Jung, S., Aucouturier, P., Littman, D.R., Cumano, A., and Geissmann, F. (2006). A clonogenic bone marrow progenitor specific for macrophages and dendritic cells. Science *311*, 83–87.

Geissmann, F., Jung, S., and Littman, D.R. (2003). Blood monocytes consist of two principal subsets with distinct migratory properties. Immunity *19*, 71–82.

Ginhoux, F., and Jung, S. (2014). Monocytes and macrophages: developmental pathways and tissue homeostasis. Nature Rev Immunol *14*, 392–404.

Goldmann T, Wieghofer P, Müller PF, Wolf Y, Varol D, Yona S, Brendecke SM, Kierdorf K, Staszewski O, Datta M, Luedde T, Heikenwalder M, Jung S, Prinz M. (2013). A new type of microglia gene targeting shows TAK1 to be pivotal in CNS autoimmune inflammation. Nat Neurosci 16(11):1618-26.

Goldmann, T., Wieghofer, P., o, M.J.C.J.A., Prutek, F., Hagemeyer, N., Frenzel, K., Amann, L., Staszewski, O., Kierdorf, K., Krueger, M., et al. (2016). Origin, fate and dynamics of macrophages at central nervous system interfaces. Nat Immunol 17(7):797-805.

Jung, S., Rajewsky, K. and A. Radbruch. Shutdown of Class Switch Recombination by deletion of switch region control element. (1993) Science. 259: 984-987.

Jung, S., Aliberti, J., Graemmel, P., Sunshine, M.J., Kreutzberg, G.W., Sher, A., and Littman, D.R. (2000). Analysis of fractalkine receptor CX(3)CR1 function by targeted deletion and green fluorescent protein reporter gene insertion. Molecular and Cellular Biology *20*, 4106–4114.

Jung, S., Unutmaz, D., Wong, P., Sano, G.-I., De los Santos, K., Sparwasser, T., Wu, S., Vuthoori, S., Ko, K., Zavala, F., et al. (2002). In vivo depletion of CD11c+ dendritic cells abrogates priming of CD8+ T cells by exogenous cell-associated antigens. Immunity *17*, 211–220.

Lavin, Y., Winter, D., Blecher-Gonen, R., David, E., Keren-Shaul, H., Merad, M., Jung, S., and Amit, I. (2014). Tissue-Resident Macrophage Enhancer Landscapes Are Shaped by the Local Microenvironment. Cell *159*, 1312–1326.

Mildner, A., Schönheit, J., Giladi, A., David, E., Lara-Astiaso, D., Lorenzo-Vivas, E., Paul, F., Chappell-Maor, L., Priller, J., Leutz, A., et al. (2017). Genomic Characterization of Murine Monocytes Reveals C/EBPβ Transcription Factor Dependence of Ly6C- Cells. Immunity *46*, 849–862.e7.

Molawi, K., Wolf, Y., Kandalla, P.K., Favret, J., Hagemeyer, N., Frenzel, K., Pinto, A.R., Klapproth, K., Henri, S., Malissen, B., et al. (2014). Progressive replacement of embryo-derived cardiac macrophages with age. J. Exp. Med. *10*, 1538.

Niess, J.H., Brand, S., Gu, X., Landsman, L., Jung, S., McCormick, B.A., Vyas, J.M., Boes, M., Ploegh, H.L., Fox, J.G., et al. (2005). CX3CR1-mediated dendritic cell access to the intestinal lumen and bacterial clearance. Science *307*, 254–258.

Varol, C., Landsman, L., Fogg, D.K., Greenshtein, L., Gildor, B., Margalit, R., Kalchenko, V., Geissmann, F., and Jung, S. (2007). Monocytes give rise to mucosal, but not splenic, conventional dendritic cells. J. Exp. Med. *204*, 171–180.

Varol, C., Vallon-Eberhard, A., Elinav, E., Aychek, T., Shapira, Y., Luche, H., Fehling, H.J., Hardt, W.-D., Shakhar, G., and Jung, S. (2009). Intestinal lamina propria dendritic cell subsets have different origin and functions. Immunity *31*, 502–512.

Varol, D., Mildner, A., Blank, T., Shemer, A., Barashi, N., Yona, S., David, E., Boura-Halfon, S., Segal-Hayoun, Y., Chappell-Maor, L., et al. (2017). Dicer Deficiency Differentially Impacts Microglia of the Developing and Adult Brain. Immunity *46*, 1030–1044.e1038.

Wolf, Y., Boura-Halfon, S., Cortese, N., Haimon, Z., Shalom, H.S., Kuperman, Y., Kalchenko, V., Brandis, A., David, E., Segal-Hayoun, Y., et al. (2017a). Brown-adipose-tissue macrophages control tissue innervation and homeostatic energy expenditure. Nat Immunol *137*, 495.

Wolf, Y., Shemer, A., Polonsky, M., Gross, M., Mildner, A., Yona, S., David, E., Kim, K.-W., Goldmann, T., Amit, I., et al. (2017b). Autonomous TNF is critical for in vivo monocyte survival in steady state and inflammation. J. Exp. Med. *69*, jem.20160499–13.

Yona, S., Kim, K.-W., Wolf, Y., Mildner, A., Varol, D., Breker, M., Strauss-Ayali, D., Viukov, S., Guilliams, M., Misharin, A., et al. (2013). Fate mapping reveals origins and dynamics of monocytes and tissue macrophages under homeostasis. Immunity *38*, 79–91.

Zigmond, E., Bernshtein, B., Friedlander, G., Walker, C.R., Yona, S., Kim, K.-W., Brenner, O., Krauthgamer, R., Varol, C., Müller, W., et al. (2014). Macrophage-restricted interleukin-10 receptor deficiency, but not IL-10 deficiency, causes severe spontaneous colitis. Immunity *40*, 720–733.

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ORCID identifier 0000-0003-4290-5716