

**Referenzen:**

Aluvihare VR, Kallikourdis M, Betz AG. Regulatory T cells mediate maternal tolerance to the fetus, *Nat Immunol* 5:266-271, 2004.

Andrew DP, Ruffing N, Kim CH, Miao W, Heath H, Li Y, Murphy K, Campbell JJ, Butcher EC, Wu L. C-C chemokine receptor 4 expression defines a major subset of circulating nonintestinal memory T cells of both Th1 and Th2 potential, *J Immunol.* 166 (1):103-111, 2001.

Arck P, Merali FS, Manuel J, Chaouat G, Clark DA. Stress-triggered abortion: Inhibition of protective suppressor mechanisms and promotion of TNF- $\alpha$  release as a mechanism triggering resorptions in mice. *Am J Reprod Immunol* 33: 74-80, 1995.

Ashkar AA, Croy BA. Functions of uterine natural killer cells are mediated by interferon gamma production during murine pregnancy, *Semin Immunol* 13 (4): 235-241, 2001.

Ashkar AA, Di Santo JP, Croy BA. Interferon gamma contributes to initiation of uterine vascular modification, decidual integrity, and uterine natural killer cell maturation during normal murine pregnancy, *J Exp Med* 192 (2):259-70, 2000.

Barber A, Robson SC, Myatt L, Bulmer J, Lyall F: Heme Oxygenase expression in human placenta and placental bed: reduced expression of placental endothelial HO-2 in pre-eclampsia and fetal growth restriction. *FASEB J* 15: 1158-1168, 2001

Bonecchi R, Bianchi G, Bordignon PP, D'Ambrosio D, Lang R, Borsatti A, Sozzani S, Allavena P, Gray PA, Mantovani A, Sinigaglia F: Differential expression of chemokine

receptors and chemotactic responsiveness of type 1 T helper cells (Th1s) and Th2s, *J Exp Med.* 187 (1): 129-134, 1998.

Brunkow ME, Jeffery EW, Hjerrild KA, Paeper B, Clark LB, Yassayko SA, Wilkinson JE, Galas D, Ziegler SF, Ramsdell F. Disruption of a new forkhead / winged helix protein, scurfin, results in the fatal lymphoproliferative disorder of the scurfy mouse, *Nature Genet* 27(1):68-73, 2001.

Chaouat G, Kolb JP, Wegmann TG. The murine placenta as an immunological barrier between the mother and the fetus, *Immunol Rev* 75:31-60, 1983.

Chaouat G, Meliani AA, Martal J, Raghupathy R, Elliot J, Mossman T, Wegmann TG: IL-10 prevents naturally occurring fetal loss in the CBA x DBA/2 mating combination, and local defect in IL-10 production in this abortion-prone combination is corrected by in vivo injection of IFN- $\tau$ . *J Immunol* 154: 4261-4268, 1995.

Chaouat G, Menu E, Clark DA, Dy M, Minkowski M, Wegmann TG: Control of fetal survival in CBA x DBA/2 mice by lymphokine therapy. *J Reprod Fertil* 89(2):447-458, 1990.

Chaouat G, Zourbas S, Ostoic S, Lappree-Delage G, Dubanchet S, Ledee N, Martal J. A brief review of recent data on some cytokine expressions at the materno-foetal interface which might challenge the classical Th1/Th2 dichotomy. *J Reprod Immunol* 53 (1-2): 241-256, 2002.

Chen HL, Kamath R, Pace JL, Russell SW, Hunt JS. Expression of the interferon-gamma receptor gene in mouse placentas is related to stage of gestation and is restricted to specific subpopulations of trophoblast cells, *Placenta* 15(2): 109-121, 1994.

Cheng HL, Schneider SL, Kane CM, Gollnick SO, Grande C, Thompson D, Pietrzak E, Tomasi TB. TGF-beta 2 gene and protein expression in maternal and fetal tissues at various stages of murine development, *J Reprod Immunol* 25 (2): 133-148, 1993.

Cobbold S, Waldmann H. Infectious tolerance, *Curr Opin Immunol* 10 (5):518-524, 1998.

Cosmi L, Liotta F, Angeli R, Mazzinghi B, Santarlasci V, Manetti R, Lasagni L, Vanini V, Romagnani P, Maggi E, Annunziato F, Romagnani S. Th2 cells are less susceptible than Th1 cells to the suppressive activity of CD25+ regulatory thymocytes because of their responsiveness to different cytokines. *Blood*. 103 (8):3117-3121, 2004.

Dünker N, Kriegstein K. TGF- $\beta$ 2-/- and 3-/- double knockout mice display severe midline fusion defects and early embryonic lethality, *Anat Embryol* 206: 73-83, 2002.

Faas MM, Schuiling GA, Baller JF, Visscher CA, Bakker WW: A new animal model for human preeclampsia: ultra-low-dose endotoxin infusion in pregnant rats. *Am J Obstet Gynecol* 171(1): 158-164, 1994.

Faas MM, Schuiling GA, Linton FA, Sargent IL, Redman CW: Activation of peripheral leukocytes in rat pregnancy and experimental preeclampsia. *Am J Obstet Gynecol* 182 (2): 351-357, 2000.

Fest S, Zenclussen AC, Joachim R, Hagen E, Busse P, Arck PC: Two Distinct Pathways Mediate Abortion in Mice: Psychoemotional Stress Acts Through CD8+ Cells Whereas Neuropeptide Substance P (SP) Mediates Inflammation via CCR5+ Cells. *Am J Reprod Immunol* 47 (6): 358, 2002.

Fontenot JD, Gavin MA, Rudensky AY. Foxp3 programs the development and function of CD4+CD25+ regulatory T cells, *Nat Immunol* 4(4):330-6, 2003.

Gorivodsky M, Torchinsky A, Zemliak I, Savion S, Fein A, Toder V: TGF beta 2 mRNA expression and pregnancy failure in mice, *Am J Reprod Immunol* 42:124-133, 1999.

Haimovici F, Hill JA, Anderson DJ. The effects of soluble products of activated lymphocytes and macrophages on blastocyst implantation events in vitro, *Biol Reprod* 44 (1): 69-75, 1991.

Hall BM, Pearce NW, Gurley KE, Dorsch SE. Specific unresponsiveness in rats with prolonged cardiac allograft survival after treatment with cyclosporine. III. Further characterization of the CD4+ suppressor cell and its mechanisms of action. *J Exp Med*. 1990 171 (1):141-57.

Hara M, Kingsley C, Niimi M, Read S, Turvey S, Bushell A, Morris P, Powrie F, Wood K: IL-10 is required for regulatory T cells to mediate tolerance to alloantigens in vivo. *J Immunol* 166: 3789-3796, 2001.

Hoffmann P, Ermann J, Edinger M, Fathmann CG, Strober S. Donor-type CD4+CD25+ regulatory T cells suppress lethal acute graft-versus-host disease after allogeneic bone marrow transplantation, *J Exp Med* 196:389-399, 2002.

Hori S, Nomura T, Sakaguchi S. Control of regulatory T cell development by transcription factor Foxp3, *Science* 299 (5609):1030-1031, 2003.

Imai T, Nagira M, Takagi S, Kakizaki M, Nishimura M, Wang J, Gray PW, Matsushima K, Yoshie O. Selective recruitment of CCR4-bearing Th2 cells toward antigen-presenting cells by the CC chemokines thymus and activation-regulated chemokine and macrophage-derived chemokine, *Int Immunol.* 11(1):81-8, 1999.

Joachim R, Oder J, Hildebrandt M, Klapp BF, Arck PC: Murine stress-triggered abortion is mediated by an increase in TNF- $\alpha$ /CD8 $^{+}$  decidual cells via Substance P. *Am J Reprod Immunol* 45 (5): 303-309, 2001.

Joachim RA, Zenclussen AC, Fest S, Douglas A, Szekeres-Bartho J, Arck PC: The progesterone Derivative Hydrogesterone Abrogates Murine Stress Triggered Abortion by Inducing a Th2 Biased Local Immune Response. *Steroids* 68 (10-13): 931-940, 2003.

Jonuleit H, Schmitt E, Kakirman H, Stassen M, Knop J, Enk AH. Infectious tolerance: human CD25 $^{+}$  regulatory T cells convey suppressor activity to conventional CD4 $^{+}$  T helper cells, *J Exp Med* 196 (2):255-260, 2002.

Khattri R, Cox T, Yasayko SA, Ramsdell F. An essential role for Scurfin in CD4+CD25+ T regulatory cells, *Nat Immunol* 4 (4):337-342, 2003.

Kingsley C, Karim M, Bushell A, Wood K: CD25+ CD4+ T regulatory cells prevent graft rejection: CTLA-4 and IL-10-Dependent Immunoregulation of alloresponses. *J Immunol* 168: 1080-1086, 2002.

Klein L, Khazaie K, von Boehmer H. In vivo dynamics of antigen-specific regulatory T cells not predicted from behavior in vitro. *Proc Natl Acad Sci U S A*. 100 (15):8886-8891, 2003.

Knackstedt MK, **Zenclussen AC**, Hertwig K, Hagen E, Dudenhausen JW, Clark DA, Arck PC. Th1 cytokines and the prothrombinase fgl2 in stress-triggered and inflammatory abortion. *Am J Reprod Immunol* 49 (4): 210-220, 2003.

Kupferminc MJ, Peaceman AM, Aderka D, Wallach D, Socol ML, Soluble tumor necrosis factor acceptors and interleukin-6 levels in patients with severe pre-eclampsia. *Obstet Gynecol* 88 (3): 420-427, 1999.

Levings MK, Sangregorio R, Roncarolo MG. Human cd25(+)cd4(+) t regulatory cells suppress naive and memory T cell proliferation and can be expanded in vitro without loss of function, *J Exp Med* 193 (11): 1295-1302, 2001.

Lin H, Mossmann TR, Guilbert L, Tuntipopipat S, Wegmann TG: Synthesis of T helper 2-type cytokines at the feto-maternal interface. *J Immunol* 151 (9): 4562-73, 1993.

Loetscher P, Uguzzoni M, Bordoli L, Baggioini M, Moser B, Chizzolini C, Dayer JM. CCR5 is characteristic of Th1 lymphocytes, *Nature* 22; 391 (6665):344-345, 1998.

Maloy KJ, Powrie F. Regulatory T cells in the control of immune pathology. *Nat Immunol.* 2 (9): 816-822, 2001.

Mantovani A, Sozzani S, Introna M: Endothelial activation by cytokines. *Ann N Y Acad Sci* 832: 93-116, 1997.

Margni RA & Zenclussen AC. During pregnancy, in the context of a Th2-type cytokine profile, serum IL-6 levels might condition the quality of the synthesized antibodies. *Am J Reprod Immunol* 46 (3): 181-189, 2001.

Margni RA, Malan Borel I: Paradoxical behavior of asymmetric IgG antibodies, *Immunol Rev* 163:77-87, 1998.

Medawar, PB: Some immunological and endocrinological problems raised by the evolution of viviparity in vertebrates. *Symp Soc Exp Bio* 44:320-338, 1953.

Nautiyal J, Kumar PG, Laloraya M. Mifepristone (Ru486) antagonizes monocyte chemotactic protein-3 down-regulation at early mouse pregnancy revealing immunomodulatory events in Ru486 induced abortion, *Am J Reprod Immunol.* 52 (1): 8-18, 2004.

Onodera K, Volk HD, Ritter T, Kupiec-Weglinski JW. Thymus requirement and antigen dependency in the "infectious" tolerance pathway in transplant recipients, *J Immunol* 160 (12): 5765-5772, 1998.

Piccinni MP, Beloni L, Livi C, Maggi E, Scarselli G, Romagnani S: Defective production of both leukemia inhibitory factor and type 2 T-helper cytokines by decidual T cells in unexplained recurrent abortions, *Nat Med* 4(9):1020-1024, 1998.

Pijnenborg R, Bland JM, Robertson WB, Brosens I. Uteroplacental arterial changes related to interstitial trophoblast migration in early human pregnancy, *Placenta* 4 (4): 397-413, 1983.

Raghupathy R, Th1-type immunity is incompatible with successful pregnancy. *Immunol Today* 10: 434-437, 1997.

Raghupathy R, Makhseed M, Azizieh F, Hassan N, Al-Azemi M, Al-Shamali E, Maternal Th1- and Th2-Type Reactivity to Placental Antigens in Normal Human Pregnancy and Unexplained Recurrent Spontaneous Abortion. *Cell Immunol* 196 (2): 122-130, 1999.

Redman CW, Sacks GP, Sargent IL: Pre-eclampsia: an excessive maternal inflammatory response to pregnancy. *Am J Obstet Gynaecol* 180 (2): 499-506, 1999.

Sacks GP, Studena K, Sargent I, Redman CWG: CD11b expression on circulating neutrophils in pre-eclampsia. *Clin Science* 93, 187-188. 1997.

Saito S, Umekage H, Sakamoto Y: Increased Th1-type immunity and decreased Th2-type immunity in patients with pre-eclampsia. *Am J Reprod Immunol* 41: 297-306, 1999 Crocker IP, Wellings RP, Fletcher J, Baker PN: Neutrophil function in women with pre-eclampsia. *Br J Obstet Gynaecol* 106 (8): 822-828, 1999.

Sakaguchi S, Sakaguchi N, Asano M, Itoh M, Toda M. Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. *J Immunol.* 155 (3):1151-1164, 1995.

Sakaguchi S, Sakaguchi N, Shimizu J, Yamazaki S, Sakihama T, Itoh M, Kuniyasu Y, Nomura T, Toda M, Takahashi T. Immunologic tolerance maintained by CD4+CD25+ regulatory T cells: their common role in controlling autoimmunity tumor immunity and transplantation tolerance, *Immunol Rev* 182:18-32, 2001.

Sasaki, Y., Sakai, M., Miyazaki, S., Higuma, S., Shiozaki, A. and Saito, S. Decidual and peripheral blood CD4+CD25+ regulatory T cells in early pregnancy subjects and spontaneous abortion cases. *Mol. Hum. Reprod.* 10: 347-353, 2004.

Sehmsdorf US, **Zenclussen AC**, Arck P, Hertwig K, Joachim RA, Klapp B, Hildebrandt MO. Human miscarriage is associated with increased number of CD26 decidual lymphocytes. *Scand J Immunol.* 4:400-407, 2004.

Sollwedel A, Zambon Bertoja A, Zenclussen ML, Gerlof K, Lisewsky U, Woiciechowsky C, Volk HD, **Zenclussen AC**. Heme Oxgenase-1 prevents murine abortion via over-expression of the cytoprotective molecule Bag-1 (eingereicht).

Sollwedel A, Zambon Bertoja A, Zenclussen ML, Ritschel S, Wollenberg I, Gerlof K, Volk HD, **Zenclussen AC**. Generation of Treg cells in the CBA/J x DBA/2J combination by vaccination with male BALB/c splenocytes rescues from abortion (eingereichtes abstract).

Somerset, D.A., Zheng, Y., Kilby, M.D., Sansom, D.M. and Drayson, M.T. Normal human pregnancy is associated with an elevation in the immune suppressive CD25+ CD4+ regulatory T-cell subset. *Immunology*. 112: 38-43, 2004.

Stephens LA, Mason D. CD25 is a marker for CD4<sup>+</sup> thymocytes that prevent autoimmune diabetes in rats, but peripheral T cells with this function are found in both CD25<sup>+</sup> and CD25<sup>-</sup> subpopulations, *J Immunol* 165:3105-3110, 2000.

Svensson L, Arvola M, Sallstrom MA, Holmdahl R, Mattsson R: The Th2 cytokines IL-4 and IL-10 are not crucial for the completion of allogeneic pregnancy in mice. *J Reprod Immunol* 51(1):3-7, 2001.

Takahashi T, Tagami T, Yamazaki S, Uede T, Shimizu J, Sakaguchi N, Mak TW, Sakaguchi S: Immunologic self-tolerance maintained by CD25(+)/CD4(+) regulatory T cells constitutively expressing cytotoxic T lymphocyte-associated antigen 4. *J.Exp.Med.* 192:303-310, 2000

Takeshita T, Satomi M, Akira S, Nakagawa Y, Takahashi H, Araki T. Preventive effect of monoclonal antibodies to intercellular adhesion molecule-1 and leukocyte function-associate antigen-1 on murine spontaneous fetal resorption. *Am J Reprod Immunol.* 43 (3): 180-185, 2000.

Tangri S, Wegmann TG, Lin H, Raghupathy R. Maternal anti-placental reactivity in natural, immunologically-mediated fetal resorptions, *J Immunol* 152 (10): 4903-4911, 1994.

Taylor P, Lees C, Blazar B: The infusion of ex vivo activated and expanded CD4+ CD25+ immune regulatory cells inhibits graft-versus-host disease lethality. *Blood* 99 (10): 3493-3499, 2002.

Tsuda H, Michimata T, Hayakawa S, Tanebe K, Sakai M, Fujimura M, Matsushima K, Saito S. A Th2 chemokine, TARC, produced by trophoblasts and endometrial gland cells, regulates the infiltration of CCR4+ T lymphocytes into human decidua at early pregnancy, *Am J Reprod Immunol.* 48(1):1-8, 2002.

Visser W, Beckmann I, Bremer HA, Lim HL, Wallenberg HC: Bioactive tumor necrosis factor alpha in pre-eclamptic patients with and without the HELLP syndrome. *Br J Obstet Gynaecol* 201 (12): 1081-1082, 1994.

Waldmann H, Graca L, Cobbold S, Adams E, Tone M, Tone Y. Regulatory T cells and organ transplantation. *Semin Immunol.* 16 (2):119-126, 2004.

Waldmann H, Graca L, Cobbold S, Adams E, Tone M, Tone Y. Regulatory T cells and organ transplantation, *Sem Immunol* 16 (2):119-126, 2004.

Wegmann T, Lin H, Guilbert L, Mossmann T, Bidirectional cytokine interactions in the maternal-fetal relationship: is successful pregnancy a Th2 phenomenon? *Immunol Today* 14: 353-356, 1993.

White CA, Johansson M, Roberts CT, Ramsay AJ, Robertson SA. Effect of Interleukin-10 null mutation on maternal immune response and reproductive outcome in mice, *Biol Reprod* 70:123-31, 2004.

Wood K and Sakaguchi S: Regulatory T cells in transplantation tolerance. *Nature Immunol* 3: 199-210, 2003.

Zambon Bertoja A, Zenclussen ML, Wollenberg I, Paeschke S, Sollwedel A, Gerlof K, Woiciechowsky C, Volk HD, **Zenclussen AC**. Up-regulation of Bcl-2 at the foetal-maternal interface from mice undergoing abortion. *Scand J Immunol* (im Druck)

**Zenclussen AC**, Mazzolli A, Kortebani G, Margni RA, Malan Borel I: IL6 and sIL6R Serum Levels in Recurrent Spontaneous Abortion Women Immnized with Paternal White Cells. *Am J Reprod Immunol*, 44: 22-29, 2000.

**Zenclussen AC**, Fest S, Sehmsdorf U-S, Hagen E, Klapp BF, Arck PC: Upregulation of Decidual P-selection Expression is Associated with an Increased Number of Th1 Cell Populations in Patients Suffering from Spontaneous Abortion. *Cell Immunol* 213 (2): 94-103, 2001a.

**Zenclussen AC**, Gentile MT, Kortebani G, Mazzolli A, Margni RA: Asymmetric antibodies and Pregnancy. *Am J Reprod Immunol* 45 (5): 289-294, 2001b.

**Zenclussen AC**, Joachim R, Hagen E, Peiser C, Klapp BF, Arck PC: Heme Oxygenase is Downregulated in Stress-Triggered and Interleukin-12-Mediated Abortion. *Scand J Immunol* 55: 560-569, 2002a.

**Zenclussen AC**, Fest S, Busse P, Joachim R, Klapp BF, Arck PC: Questioning the Th1/Th2 paradigm: Peripheral Levels of IL-12 are Downregulated in Miscarriage Patients. *Am J Reprod Immunol* 48 (4):245-251, 2002b.

**Zenclussen AC**, Lim E, Knoeller S, Knackstedt M, Hertwig K, Klapp BF, Arck PC: Heme Oxygenases in Pregnancy II: HO-2 is Downregulated During Human Failing Pregnancies. *Am J Reprod Immunol* 50 (1): 66-76, 2003a.

**Zenclussen AC**, Blois S, Olmos S, Roux ME, Margni RA. Murine abortion is associated with enhanced Interleukin-6 levels at the feto-maternal interface. *Cytokine* 24: 150-160, 2003b.

**Zenclussen AC**, Zambon Bertoja A, Sollwedel A, Leber J, Zenclussen ML, Paeschke S, Woiciechowsky C, Volk H-D: Ex-vivo production of Th1 and Th2 cytokines as well as chemokine receptors expression by decidual and placental cells in an immunological abortion mouse model. *Immunobiology* 208 (1-3): 307-308. 2003c.

**Zenclussen AC**, Fest S, Joachim R, Klapp BF, Arck PC: Introducing a novel model for pre-eclampsia: Adoptive transfer of Th1-activated cells leads to pre-eclampsia like symptoms exclusively in pregnant mice *Eur J Immunol* 34 (2): 377-387, 2004.

**Zenclussen AC**, Sollwedel A, Zambon Bertoja A, Gerlof K, Zenclussen ML, Woiciechowsky C, Volk HD. Heme Oxygenase as a therapeutic target in immunological pregnancy complications *Int Immunopharmacol* 5 (1): 41-51, 2005a.

**Zenclussen AC**, Gerlof K, Zenclussen ML, Bertoja A, Sollwedel A, Ritter T, Kotsch K, Leber J, Volk HD. Abormal T cell reactivity against paternal antigens: The adoptive transfer

of CD4<sup>+</sup>CD25<sup>+</sup> T regulatory cells prevents fetal rejection by diminishing Ag-specific Th1 cytokines production in a murine abortion model. *Am J Pathol* 166 (3): 811-822, 2005b.

**Zenclussen AC.** CD4(+)CD25+ T regulatory cells in murine pregnancy. *J Reprod Immunol.* 65 (2): 101-110, 2005c.

**Zenclussen AC**, Gerlof K, Zambon Bertoja A, Zenclussen ML, Ritschel S, Hontsu S, Ueha S, Matushima K, Sollwedel A, Woiciechowsky C, Volk HD. Unraveling the molecular mechanisms involved in CD4<sup>+</sup>CD25<sup>+</sup> T regulatory cells-induced pregnancy protection: Treg cells induce a privileged tolerant microenvironment at the fetal-maternal interface by up-regulating HO-1, TGF-β and LIF expression (eingereicht).

Zenclussen ML, Anegon I, Zambon Bertoja A, Chauveau C, Vogt K, Gerlof K, Sollwedel A, Volk HD, Ritter T, **Zenclussen AC**. Upregulation of Heme Oxygenase-1 by adenoviral gene transfer improves pregnancy outcome in a murine model of abortion (in finaler Begutachtung).

Zingoni A, Soto H, Hedrick JA, Stoppacciaro A, Storlazzi CT, Sinigaglia F, D'Ambrosio D, O'Garra A, Robinson D, Rocchi M, Santoni A, Zlotnik A, Napolitano M. The chemokine receptor CCR8 is preferentially expressed in Th2 but not Th1 cells, *J Immunol* 161 (2): 547-551, 1998.