

## 7 Literaturverzeichnis

1. Tan EM, Cohen AS, Fries JF, et al. (1982) The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 25: 1271-1277.
2. Hochberg MC. (1997) Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 40: 1725.
3. Deapen D, Escalante A, Weinrib L, et al. (1992) A revised estimate of twin concordance in systemic lupus erythematosus. *Arthritis Rheum* 35: 311-318.
4. Mohan C, Morel L, Yang P, et al. (1999) Genetic dissection of lupus pathogenesis: a recipe for nephrophilic autoantibodies. *J Clin Invest* 103: 1685-1695.
5. Mohan C, Yu Y, Morel L, Yang P, Wakeland EK. (1999) Genetic dissection of Sle pathogenesis: Sle3 on murine chromosome 7 impacts T cell activation, differentiation, and cell death. *J Immunol* 162: 6492-6502.
6. Hahn B. (2002) An overview of the pathogenesis of systemic lupus erythematosus. In: Wallace DJ HB (ed.) *Dubois' Lupus Erythematosus*. Lippincott Williams&Wilkins, Philadelphia, pp. 87-96.
7. Taylor PR, Carugati A, Fadok VA, et al. (2000) A hierarchical role for classical pathway complement proteins in the clearance of apoptotic cells in vivo. *J Exp Med* 192: 359-366.
8. Robson MG, Walport MJ. (2001) Pathogenesis of systemic lupus erythematosus (SLE). *Clin Exp Allergy* 31: 678-685.
9. James JA, Kaufman KM, Farris AD, Taylor-Albert E, Lehman TJ, Harley JB. (1997) An increased prevalence of Epstein-Barr virus infection in young patients suggests a possible etiology for systemic lupus erythematosus. *J Clin Invest* 100: 3019-3026.
10. James JA, Neas BR, Moser KL, et al. (2001) Systemic lupus erythematosus in adults is associated with previous Epstein-Barr virus exposure. *Arthritis Rheum* 44: 1122-1126.
11. Pramatarov KD. (1998) Drug-induced lupus erythematosus. *Clin Dermatol* 16: 367-377.
12. Cohen PL, Eisenberg RA. (1992) The *lpr* and *gld* genes in systemic autoimmunity: life and death in the Fas lane. *Immunol Today* 13: 427-428.
13. Strasser A, Whittingham S, Vaux DL, et al. (1991) Enforced BCL2 expression in B-lymphoid cells prolongs antibody responses and elicits autoimmune disease. *Proc Natl Acad Sci U S A* 88: 8661-8665.
14. Bouillet P, Metcalf D, Huang DC, et al. (1999) Proapoptotic Bcl-2 relative Bim required for certain apoptotic responses, leukocyte homeostasis, and to preclude autoimmunity. *Science* 286: 1735-1738.
15. Raptis L, Menard HA. (1980) Quantitation and characterization of plasma DNA in normals and patients with systemic lupus erythematosus. *J Clin Invest* 66: 1391-1399.
16. Rumore PM, Steinman CR. (1990) Endogenous circulating DNA in systemic lupus erythematosus. Occurrence as multimeric complexes bound to histone. *J Clin Invest* 86: 69-74.
17. Casciola-Rosen LA, Anhalt G, Rosen A. (1994) Autoantigens targeted in systemic lupus erythematosus are clustered in two populations of surface structures on apoptotic keratinocytes. *J Exp Med* 179: 1317-1330.
18. Mohan C, Adams S, Stanik V, Datta SK. (1993) Nucleosome: a major immunogen for pathogenic autoantibody-inducing T cells of lupus. *J Exp Med* 177: 1367-1381.
19. Emlen W, Niebur J, Kadera R. (1994) Accelerated in vitro apoptosis of lymphocytes from patients with systemic lupus erythematosus. *J Immunol* 152: 3685-3692.
20. Bijl M, Horst G, Limburg PC, Kallenberg CG. (2001) Anti-CD3-induced and anti-Fas-induced apoptosis in systemic lupus erythematosus (SLE). *Clin Exp Immunol* 123: 127-132.
21. Herrmann M, Voll RE, Zoller OM, Hagenhofer M, Ponner BB, Kalden JR. (1998) Impaired phagocytosis of apoptotic cell material by monocyte-derived macrophages from patients with systemic lupus erythematosus. *Arthritis Rheum* 41: 1241-1250.
22. Baumann I, Kolowos W, Voll RE, et al. (2002) Impaired uptake of apoptotic cells into tingible body macrophages in germinal centers of patients with systemic lupus

- erythematosus. *Arthritis Rheum* 46: 191-201.
23. Voll RE, Herrmann M, Roth EA, Stach C, Kalden JR, Girkontaite I. (1997) Immunosuppressive effects of apoptotic cells. *Nature* 390: 350-351.
  24. Fadok VA, Bratton DL, Konowal A, Freed PW, Westcott JY, Henson PM. (1998) Macrophages that have ingested apoptotic cells in vitro inhibit proinflammatory cytokine production through autocrine/paracrine mechanisms involving TGF-beta, PGE2, and PAF. *J Clin Invest* 101: 890-898.
  25. Manfredi AA, Rovere P, Galati G, et al. (1998) Apoptotic cell clearance in systemic lupus erythematosus. I. Opsonization by antiphospholipid antibodies. *Arthritis Rheum* 41: 205-214.
  26. Hahn BH, Singh RR, Ebling FM. (1998) Self Ig peptides that help anti-DNA antibody production: importance of charged residues. *Lupus* 7: 307-313.
  27. Mamula MJ, Lin RH, Janeway CA, Jr., Hardin JA. (1992) Breaking T cell tolerance with foreign and self co-immunogens. A study of autoimmune B and T cell epitopes of cytochrome c. *J Immunol* 149: 789-795.
  28. Lin RH, Mamula MJ, Hardin JA, Janeway CA, Jr. (1991) Induction of autoreactive B cells allows priming of autoreactive T cells. *J Exp Med* 173: 1433-1439.
  29. Chan OT, Hannum LG, Haberman AM, Madaio MP, Shlomchik MJ. (1999) A novel mouse with B cells but lacking serum antibody reveals an antibody-independent role for B cells in murine lupus. *J Exp Med* 189: 1639-1648.
  30. Chan OT, Madaio MP, Shlomchik MJ. (1999) The central and multiple roles of B cells in lupus pathogenesis. *Immunol Rev* 169: 107-121.
  31. Liossis SNC GC. (2002) B-cell abnormalities in systemic lupus erythematosus. In: Wallace DJ HB (ed.) *Dubois' Lupus Erythematosus*. Lippincott Williams&Wilkins, Philadelphia.
  32. Liossis SN, Kovacs B, Dennis G, Kammer GM, Tsokos GC. (1996) B cells from patients with systemic lupus erythematosus display abnormal antigen receptor-mediated early signal transduction events. *J Clin Invest* 98: 2549-2557.
  33. Kitani A, Hara M, Hirose T, et al. (1992) Autostimulatory effects of IL-6 on excessive B cell differentiation in patients with systemic lupus erythematosus: analysis of IL-6 production and IL-6R expression. *Clin Exp Immunol* 88: 75-83.
  34. Llorente L, Zou W, Levy Y, et al. (1995) Role of interleukin 10 in the B lymphocyte hyperactivity and autoantibody production of human systemic lupus erythematosus. *J Exp Med* 181: 839-844.
  35. Radic MZ, Weigert M. (1994) Genetic and structural evidence for antigen selection of anti-DNA antibodies. *Annu Rev Immunol* 12: 487-520.
  36. Monestier M. (1991) Variable region genes of anti-histone autoantibodies from a MRL/Mp-lpr/lpr mouse. *Eur J Immunol* 21: 1725-1731.
  37. Burlingame RW, Rubin RL, Balderas RS, Theofilopoulos AN. (1993) Genesis and evolution of antichromatin autoantibodies in murine lupus implicates T-dependent immunization with self antigen. *J Clin Invest* 91: 1687-1696.
  38. Riemekasten G, Marell J, Trebeljahr G, et al. (1998) A novel epitope on the C-terminus of SmD1 is recognized by the majority of sera from patients with systemic lupus erythematosus. *J Clin Invest* 102: 754-763.
  39. Steinberg AD, Roths JB, Murphy ED, Steinberg RT, Raveche ES. (1980) Effects of thymectomy or androgen administration upon the autoimmune disease of MRL/Mp-lpr/lpr mice. *J Immunol* 125: 871-873.
  40. Mihara M, Ohsugi Y, Saito K, et al. (1988) Immunologic abnormality in NZB/NZW F1 mice. Thymus-independent occurrence of B cell abnormality and requirement for T cells in the development of autoimmune disease, as evidenced by an analysis of the athymic nude individuals. *J Immunol* 141: 85-90.
  41. Wofsy D, Seaman WE. (1987) Reversal of advanced murine lupus in NZB/NZW F1 mice by treatment with monoclonal antibody to L3T4. *J Immunol* 138: 3247-3253.
  42. Lorenz HM, Herrmann M, Winkler T, Gaipf U, Kalden JR. (2000) Role of apoptosis in autoimmunity. *Apoptosis* 5: 443-449.

43. Linker-Israeli M, Quismorio FP, Jr., Horwitz DA. (1990) CD8+ lymphocytes from patients with systemic lupus erythematosus sustain, rather than suppress, spontaneous polyclonal IgG production and synergize with CD4+ cells to support autoantibody synthesis. *Arthritis Rheum* 33: 1216-1225.
44. Lewinsohn DM, Bement TT, Xu J, et al. (1998) Human purified protein derivative-specific CD4+ T cells use both CD95-dependent and CD95-independent cytolytic mechanisms. *J Immunol* 160: 2374-2379.
45. Ohashi PS, Oehen S, Buerki K, et al. (1991) Ablation of "tolerance" and induction of diabetes by virus infection in viral antigen transgenic mice. *Cell* 65: 305-317.
46. Kammer GM, Perl A, Richardson BC, Tsokos GC. (2002) Abnormal T cell signal transduction in systemic lupus erythematosus. *Arthritis Rheum* 46: 1139-1154.
47. Kaliyaperumal A, Michaels MA, Datta SK. (2002) Naturally processed chromatin peptides reveal a major autoepitope that primes pathogenic T and B cells of lupus. *J Immunol* 168: 2530-2537.
48. Kaliyaperumal A, Mohan C, Wu W, Datta SK. (1996) Nucleosomal peptide epitopes for nephritis-inducing T helper cells of murine lupus. *J Exp Med* 183: 2459-2469.
49. Freed JH, Marrs A, VanderWall J, Cohen PL, Eisenberg RA. (2000) MHC class II-bound self peptides from autoimmune MRL/lpr mice reveal potential T cell epitopes for autoantibody production in murine systemic lupus erythematosus. *J Immunol* 164: 4697-4705.
50. Monneaux F, Dumortier H, Steiner G, Briand JP, Muller S. (2001) Murine models of systemic lupus erythematosus: B and T cell responses to spliceosomal ribonucleoproteins in MRL/Fas(lpr) and (NZB x NZW)F(1) lupus mice. *Int Immunol* 13: 1155-1163.
51. Riemekasten G, Langnickel D, Ebling FM, et al. (2003) Identification and characterization of SmD183-119-reactive T cells that provide T cell help for pathogenic anti-double-stranded DNA antibodies. *Arthritis Rheum* 48: 475-485.
52. Riemekasten G, Kawald A, Weiss C, et al. (2001) Strong acceleration of murine lupus by injection of the SmD1(83-119) peptide. *Arthritis Rheum* 44: 2435-2445.
53. Kaliyaperumal A, Michaels MA, Datta SK. (1999) Antigen-specific therapy of murine lupus nephritis using nucleosomal peptides: tolerance spreading impairs pathogenic function of autoimmune T and B cells. *J Immunol* 162: 5775-5783.
54. Singh RR, Ebling FM, Sercarz EE, Hahn BH. (1995) Immune tolerance to autoantibody-derived peptides delays development of autoimmunity in murine lupus. *J Clin Invest* 96: 2990-2996.
55. Liblau R, Tisch R, Bercovici N, McDevitt HO. (1997) Systemic antigen in the treatment of T-cell-mediated autoimmune diseases. *Immunol Today* 18: 599-604.
56. Thorstenson KM, Khoruts A. (2001) Generation of anergic and potentially immunoregulatory CD25+CD4 T cells in vivo after induction of peripheral tolerance with intravenous or oral antigen. *J Immunol* 167: 188-195.
57. Yasuma M, Takasaki Y, Matsumoto K, Kodama A, Hashimoto H, Hirose S. (1990) Clinical significance of IgG anti-Sm antibodies in patients with systemic lupus erythematosus. *J Rheumatol* 17: 469-475.
58. Takeda Y, Wang GS, Wang RJ, et al. (1989) Enzyme-linked immunosorbent assay using isolated (U) small nuclear ribonucleoprotein polypeptides as antigens to investigate the clinical significance of autoantibodies to these polypeptides. *Clin Immunol Immunopathol* 50: 213-230.
59. Hiepe F, Kiessig ST, Yamamoto K, et al. (1990) [Detection of autoantibodies to extractable nuclear antigens in autoimmune diseases of rheumatic origin using immunoblotting-comparison with counter-electrophoresis]. *Z Rheumatol* 49: 304-309.
60. Abuaf N, Johanet C, Chretien P, Absalon BI, Homberg JC, Buri JF. (1990) Detection of autoantibodies to Sm antigen in systemic lupus erythematosus by immunodiffusion, ELISA and immunoblotting: variability of incidence related to assays and ethnic origin of patients. *Eur J Clin Invest* 20: 354-359.
61. Black DL, Chabot B, Steitz JA. (1985) U2 as well as U1 small nuclear

- ribonucleoproteins are involved in premessenger RNA splicing. *Cell* 42: 737-750.
62. Rogers J, Wall R. (1980) A mechanism for RNA splicing. *Proc Natl Acad Sci U S A* 77: 1877-1879.
  63. Seraphin B. (1995) Sm and Sm-like proteins belong to a large family: identification of proteins of the U6 as well as the U1, U2, U4 and U5 snRNPs. *Embo J* 14: 2089-2098.
  64. Salgado-Garrido J, Bragado-Nilsson E, Kandels-Lewis S, Seraphin B. (1999) Sm and Sm-like proteins assemble in two related complexes of deep evolutionary origin. *Embo J* 18: 3451-3462.
  65. Mattioli M, Reichlin M. (1971) Characterization of a soluble nuclear ribonucleoprotein antigen reactive with SLE sera. *J Immunol* 107: 1281-1290.
  66. Cameron JS. (1999) Lupus nephritis. *J Am Soc Nephrol* 10: 413-424.
  67. Mills JA. (1994) Systemic lupus erythematosus. *N Engl J Med* 330: 1871-1879.
  68. (2000) Basislehrbuch Innere Medizin. In: Renz-polster H BJ (ed.). Urban&Fischer, München Jena.
  69. (1999) Allgemeine und spezielle Pathologie. In: Riede UN SH (ed.). Thieme, Stuttgart - New York.
  70. (1994) Klinische Pathophysiologie. In: W S (ed.) *Klinische Pathophysiologie*. Thieme, Stuttgart - New York.
  71. Amoura Z, Chabre H, Koutouzov S, et al. (1994) Nucleosome-restricted antibodies are detected before anti-dsDNA and/or antihistone antibodies in serum of MRL-Mp lpr/lpr and +/+ mice, and are present in kidney eluates of lupus mice with proteinuria. *Arthritis Rheum* 37: 1684-1688.
  72. Theofilopoulos AN, Dixon FJ. (1985) Murine models of systemic lupus erythematosus. *Adv Immunol* 37: 269-390.
  73. Schur PH, Sandson J. (1968) Immunologic factors and clinical activity in systemic lupus erythematosus. *N Engl J Med* 278: 533-538.
  74. Smeenk RJ, van den Brink HG, Brinkman K, Termaat RM, Berden JH, Swaak AJ. (1991) Anti-dsDNA: choice of assay in relation to clinical value. *Rheumatol Int* 11: 101-107.
  75. Weinstein A, Bordwell B, Stone B, Tibbetts C, Rothfield NF. (1983) Antibodies to native DNA and serum complement (C3) levels. Application to diagnosis and classification of systemic lupus erythematosus. *Am J Med* 74: 206-216.
  76. Hahn BH. (1998) Antibodies to DNA. *N Engl J Med* 338: 1359-1368.
  77. Ohnishi K, Ebling FM, Mitchell B, Singh RR, Hahn BH, Tsao BP. (1994) Comparison of pathogenic and non-pathogenic murine antibodies to DNA: antigen binding and structural characteristics. *Int Immunol* 6: 817-830.
  78. Ehrenstein MR, Katz DR, Griffiths MH, et al. (1995) Human IgG anti-DNA antibodies deposit in kidneys and induce proteinuria in SCID mice. *Kidney Int* 48: 705-711.
  79. Amoura Z, Piette JC, Bach JF, Koutouzov S. (1999) The key role of nucleosomes in lupus. *Arthritis Rheum* 42: 833-843.
  80. van Bruggen MC, Kramers K, Hylkema MN, et al. (1995) Decrease of heparan sulfate staining in the glomerular basement membrane in murine lupus nephritis. *Am J Pathol* 146: 753-763.
  81. Bernstein KA, Valerio RD, Lefkowitz JB. (1995) Glomerular binding activity in MRL lpr serum consists of antibodies that bind to a DNA/histone/type IV collagen complex. *J Immunol* 154: 2424-2433.
  82. Lefkowitz JB, Kiehl M, Rubenstein J, et al. (1996) Heterogeneity and clinical significance of glomerular-binding antibodies in systemic lupus erythematosus. *J Clin Invest* 98: 1373-1380.
  83. Mostoslavsky G, Fischel R, Yachimovich N, et al. (2001) Lupus anti-DNA autoantibodies cross-react with a glomerular structural protein: a case for tissue injury by molecular mimicry. *Eur J Immunol* 31: 1221-1227.
  84. Yanase K, Smith RM, Puccetti A, Jarett L, Madaio MP. (1997) Receptor-mediated cellular entry of nuclear localizing anti-DNA antibodies via myosin 1. *J Clin Invest* 100:

- 25-31.
85. Koren E, Koscec M, Wolfson-Reichlin M, et al. (1995) Murine and human antibodies to native DNA that cross-react with the A and D SnRNP polypeptides cause direct injury of cultured kidney cells. *J Immunol* 154: 4857-4864.
  86. Boucher A, Droz D, Adafer E, Noel LH. (1986) Characterization of mononuclear cell subsets in renal cellular interstitial infiltrates. *Kidney Int* 29: 1043-1049.
  87. Caligaris-Cappio F, Bergui L, Tesio L, Ziano R, Camussi G. (1985) HLA-Dr+ T cells of the Leu 3 (helper) type infiltrate the kidneys of patients with systemic lupus erythematosus. *Clin Exp Immunol* 59: 185-189.
  88. Alexopoulos E, Seron D, Hartley RB, Cameron JS. (1990) Lupus nephritis: correlation of interstitial cells with glomerular function. *Kidney Int* 37: 100-109.
  89. Jeruc J, Jurcic V, Vizjak A, et al. (2000) Tubulo-interstitial involvement in lupus nephritis with emphasis on pathogenesis. *Wien Klin Wochenschr* 112: 702-706.
  90. Masutani K, Akahoshi M, Tsuruya K, et al. (2001) Predominance of Th1 immune response in diffuse proliferative lupus nephritis. *Arthritis Rheum* 44: 2097-2106.
  91. D'Agati VD, Appel GB, Estes D, Knowles DM, 2nd, Pirani CL. (1986) Monoclonal antibody identification of infiltrating mononuclear leukocytes in lupus nephritis. *Kidney Int* 30: 573-581.
  92. Yamada M, Yagita H, Inoue H, et al. (2002) Selective accumulation of CCR4+ T lymphocytes into renal tissue of patients with lupus nephritis. *Arthritis Rheum* 46: 735-740.
  93. Segerer S, Mac KM, Regele H, Kerjaschki D, Schlondorff D. (1999) Expression of the C-C chemokine receptor 5 in human kidney diseases. *Kidney Int* 56: 52-64.
  94. Diaz Gallo C, Jevnikar AM, Brennan DC, Florquin S, Pacheco-Silva A, Kelley VR. (1992) Autoreactive kidney-infiltrating T-cell clones in murine lupus nephritis. *Kidney Int* 42: 851-859.
  95. Cassese G, Lindenau S, de Boer B, et al. (2001) Inflamed kidneys of NZB / W mice are a major site for the homeostasis of plasma cells. *Eur J Immunol* 31: 2726-2732.
  96. Park MH, D'Agati V, Appel GB, Pirani CL. (1986) Tubulointerstitial disease in lupus nephritis: relationship to immune deposits, interstitial inflammation, glomerular changes, renal function, and prognosis. *Nephron* 44: 309-319.
  97. Magil AB, Tyler M. (1984) Tubulo-interstitial disease in lupus nephritis. A morphometric study. *Histopathology* 8: 81-87.
  98. Schwartz M, Fennell J, Lewis E. (1982) Pathologic changes in the renal tubule in systemic lupus erythematosus. *Hum Pathol.* 13: 534-547.
  99. Hurd E, Ziff M. (1978) Association of interstitial nephritis with tubule cell injury and proliferation in NZB/NZW mice. *Clin Exp Immunol.* 32: 1-11.
  100. Kelley VR, Diaz-Gallo C, Jevnikar AM, Singer GG. (1993) Renal tubular epithelial and T cell interactions in autoimmune renal disease. *Kidney Int Suppl* 39: S108-115.
  101. Massengill S, Goodenow M, Sleasman J. (1998) SLE nephritis is associated with an oligoclonal expansion of intrarenal T cells. *Am J Kidney Dis.* 31: 418-426.
  102. Murata H, Matsumura R, Koyama A, et al. (2002) T cell receptor repertoire of T cells in the kidneys of patients with lupus nephritis. *Arthritis Rheum.* 46: 2141-2147.
  103. Kuroiwa T, Lee E. (1998) Cellular interactions in the pathogenesis of lupus nephritis: the role of T cells and macrophages in the amplification of the inflammatory process in the kidney. *Lupus* 7: 597-603.
  104. Kupp L, Kosco M, Schenkein H, Tew J. (1991) Chemotaxis of germinal center B cells in response to C5a. *Eur J Immunol* 21: 2697-2701.
  105. Kim H, Krenn V, Steinhauser G, Berek C. (1999) Plasma cell development in synovial germinal centers in patients with rheumatoid and reactive arthritis. *J Immunol* 162: 3053-3062.
  106. William J, Euler C, Christensen S, Shlomchik M. (2002) Evolution of autoantibody responses via somatic hypermutation outside of germinal centers. *Science* 297: 2066-2070.

107. Fu Y, Storb U. (2002) Immunology. Autoreactive B cells migrate into T cell territory. *Science*. 297: 2006-2008.
108. Hahn B. (1993) Animal Models of Systemic Lupus Erythematosus. In: Wallace DJ HB (ed.) *Dubois' Lupus erythematosus*. Lea & Febiger.
109. Janeway CA TP. (1997) Immunologie. Spektrum Akademischer Verlag.
110. Stoll ML, Gavalchin J. (2000) Systemic lupus erythematosus-messages from experimental models. *Rheumatology (Oxford)* 39: 18-27.
111. Schwarting A, Tesch G, Kinoshita K, Maron R, Weiner HL, Kelley VR. (1999) IL-12 drives IFN-gamma-dependent autoimmune kidney disease in MRL-Fas(lpr) mice. *J Immunol* 163: 6884-6891.
112. Eisenberg RA, Tan EM, Dixon FJ. (1978) Presence of anti-Sm reactivity in autoimmune mouse strains. *J Exp Med* 147: 582-587.
113. Ziegler SF, Ramsdell F, Alderson MR. (1994) The activation antigen CD69. *Stem Cells* 12: 456-465.
114. Sakaguchi S, Sakaguchi N, Asano M, Itoh M, Toda M. (1995) 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: 1151-1164.
115. Bryl E, Vallejo AN, Weyand CM, Goronzy JJ. (2001) Down-regulation of CD28 expression by TNF-alpha. *J Immunol* 167: 3231-3238.
116. Vallejo AN, Brandes JC, Weyand CM, Goronzy JJ. (1999) Modulation of CD28 expression: distinct regulatory pathways during activation and replicative senescence. *J Immunol* 162: 6572-6579.
117. Schmidt D, Goronzy JJ, Weyand CM. (1996) CD4+ CD7- CD28- T cells are expanded in rheumatoid arthritis and are characterized by autoreactivity. *J Clin Invest* 97: 2027-2037.
118. Sfrikakis PP, Via CS. (1997) Expression of CD28, CTLA4, CD80, and CD86 molecules in patients with autoimmune rheumatic diseases: implications for immunotherapy. *Clin Immunol Immunopathol* 83: 195-198.
119. Sprent J, Tough DF. (1994) Lymphocyte life-span and memory. *Science* 265: 1395-1400.
120. Bradley LM, Croft M, Swain SL. (1993) T-cell memory: new perspectives. *Immunol Today* 14: 197-199.
121. Budd RC, Cerottini JC, Horvath C, et al. (1987) Distinction of virgin and memory T lymphocytes. Stable acquisition of the Pgp-1 glycoprotein concomitant with antigenic stimulation. *J Immunol* 138: 3120-3129.
122. Mosmann TR, Coffman RL. (1989) TH1 and TH2 cells: different patterns of lymphokine secretion lead to different functional properties. *Annu Rev Immunol* 7: 145-173.
123. Trinchieri G. (2001) Regulatory role of T cells producing both interferon gamma and interleukin 10 in persistent infection. *J Exp Med* 194: F53-57.
124. Dang H, Harbeck RJ. (1982) A comparison of anti-DNA antibodies from serum and kidney eluates of NZB x NZW F1 mice. *J Clin Lab Immunol* 9: 139-145.
125. Koshy M, Berger D, Crow MK. (1996) Increased expression of CD40 ligand on systemic lupus erythematosus lymphocytes. *J Clin Invest* 98: 826-837.
126. Caruso A, Licenziati S, Corulli M, et al. (1997) Flow cytometric analysis of activation markers on stimulated T cells and their correlation with cell proliferation. *Cytometry* 27: 71-76.
127. Biselli R, Matricardi PM, D'Amelio R, Fattorossi A. (1992) Multiparametric flow cytometric analysis of the kinetics of surface molecule expression after polyclonal activation of human peripheral blood T lymphocytes. *Scand J Immunol* 35: 439-447.
128. Testi R, Phillips JH, Lanier LL. (1989) Leu 23 induction as an early marker of functional CD3/T cell antigen receptor triggering. Requirement for receptor cross-linking, prolonged elevation of intracellular [Ca<sup>++</sup>] and stimulation of protein kinase C. *J Immunol* 142: 1854-1860.

129. Ishikawa S, Akakura S, Abe M, et al. (1998) A subset of CD4+ T cells expressing early activation antigen CD69 in murine lupus: possible abnormal regulatory role for cytokine imbalance. *J Immunol* 161: 1267-1273.
130. Afeltra A, Galeazzi M, Ferri GM, et al. (1993) Expression of CD69 antigen on synovial fluid T cells in patients with rheumatoid arthritis and other chronic synovitis. *Ann Rheum Dis* 52: 457-460.
131. Garcia-Monzon C, Moreno-Otero R, Pajares JM, et al. (1990) Expression of a novel activation antigen on intrahepatic CD8+ T lymphocytes in viral chronic active hepatitis. *Gastroenterology* 98: 1029-1035.
132. Tough DF, Sun S, Zhang X, Sprent J. (1999) Stimulation of naive and memory T cells by cytokines. *Immunol Rev* 170: 39-47.
133. Hesse MD, Karulin AY, Boehm BO, Lehmann PV, Tary-Lehmann M. (2001) A T cell clone's avidity is a function of its activation state. *J Immunol* 167: 1353-1361.
134. Shevach EM. (2002) CD4+ CD25+ suppressor T cells: more questions than answers. *Nat Rev Immunol* 2: 389-400.
135. Crispin JC, Martinez A, Alcocer-Varela J. (2003) Quantification of regulatory T cells in patients with systemic lupus erythematosus. *J Autoimmun* 21: 273-276.
136. Liu MF, Wang CR, Fung LL, Wu CR. (2004) Decreased CD4+CD25+ T cells in peripheral blood of patients with systemic lupus erythematosus. *Scand J Immunol* 59: 198-202.
137. Barnes D, Sato G. (1980) Methods for growth of cultured cells in serum-free medium. *Anal Biochem* 102: 255-270.
138. Knapp W, Rieber P, Dorken B, Schmidt RE, Stein H, vd Borne AE. (1989) Towards a better definition of human leucocyte surface molecules. *Immunol Today* 10: 253-258.
139. Pelosi E, Testa U, Louache F, et al. (1986) Expression of transferrin receptors in phytohemagglutinin-stimulated human T-lymphocytes. Evidence for a three-step model. *J Biol Chem* 261: 3036-3042.
140. Bijl M, Horst G, Limburg PC, Kallenberg CG. (2001) Expression of costimulatory molecules on peripheral blood lymphocytes of patients with systemic lupus erythematosus. *Ann Rheum Dis* 60: 523-526.
141. Denfeld RW, Kind P, Sontheimer RD, Schopf E, Simon JC. (1997) In situ expression of B7 and CD28 receptor families in skin lesions of patients with lupus erythematosus. *Arthritis Rheum* 40: 814-821.
142. Gringhuis SI, Leow A, Papendrecht-Van Der Voort EA, Remans PH, Breedveld FC, Verweij CL. (2000) Displacement of linker for activation of T cells from the plasma membrane due to redox balance alterations results in hyporesponsiveness of synovial fluid T lymphocytes in rheumatoid arthritis. *J Immunol* 164: 2170-2179.
143. Maurice MM, Lankester AC, Bezemer AC, et al. (1997) Defective TCR-mediated signaling in synovial T cells in rheumatoid arthritis. *J Immunol* 159: 2973-2978.
144. Abbas AK, Lichtman AH. (2003) Cellular and Molecular Immunology. W B Saunders, Philadelphia.
145. Bell EB, Sparshott SM. (1990) Interconversion of CD45R subsets of CD4 T cells in vivo. *Nature* 348: 163-166.
146. Rothstein DM, Yamada A, Schlossman SF, Morimoto C. (1991) Cyclic regulation of CD45 isoform expression in a long term human CD4+CD45RA+ T cell line. *J Immunol* 146: 1175-1183.
147. Neidhart M, Pataki F, Michel BA, Fehr K. (1996) CD45 isoforms expression on CD4+ and CD8+ peripheral blood T-lymphocytes is related to auto-immune processes and hematological manifestations in systemic lupus erythematosus. *Schweiz Med Wochenschr* 126: 1922-1925.
148. Gordon C, Matthews N, Schlesinger BC, et al. (1996) Active systemic lupus erythematosus is associated with the recruitment of naive/resting T cells. *Br J Rheumatol* 35: 226-230.
149. Chu EB, Ernst DN, Hobbs MV, Weigle WO. (1994) Maturation changes in CD4+ cell subsets and lymphokine production in BXSb mice. *J Immunol* 152: 4129-4138.

150. Cope AP. (2002) Studies of T-cell activation in chronic inflammation. *Arthritis Res* 4 Suppl 3: S197-211.
151. Makinodan T, Kay MM. (1980) Age influence on the immune system. *Adv Immunol* 29: 287-330.

## 8 Anhang

### 8.1 Abkürzungsverzeichnis

AFC	Antibody forming cell (ein Spot beim ELISPOT Essay)
Ak	Antikörper
AP	Alkalischer Phosphatase
APC	Antigen-präsentierende-Zelle
BSA	Bovines Serum-Albumin
BWF1	Weibliche Nachkommenschaft der ersten Filialgeneration von New Zealand Black (NZB) und New Zealand White (NZW) Mäusen
CD	Cluster of Differentiation
CRP	C-reaktives Protein
Cy5	Fluoreszenzfarbstoff
dsDNA	Doppelsträngige DNA
ELISA	Enzyme linked immunosorbent assay
ELISPOT	Enzyme-linked immunospot assay
DIG	Digoxygenin
DIG-Cy5	Kombination eines DIG gekoppelten Primärantikörpers mit einem Cy5 gekoppelten Nachweisantikörper zur Färbung von Zellen für die FACS Analyse
FCS	Forwards Scatter, Vorwärtsstreulicht bei der Durchflusszytometrie
FITC	Fluoreszenzfarbstoff
Hb	Hämoglobin
IC	Immunkomplexe
ICAM	Intercellular Cell Adhesion Molecule (Adhäsionsmolekül)
IFN	Interferon
Ig	Immunglobulin (=Antikörper)
IL	Interleukin
MHC	Major Histocompatibility Complex

MRL/lpr	MRL Mäuse, welche homozygot für die <i>lpr</i> Mutation tragen; <i>lpr</i> steht für Lymphoproliferation.
MW	Mittelwert
NZB/NZW F1	Weibliche Nachkommenschaft der ersten Filialgeneration von New Zealand Black (NZB) und New Zealand White (NZW) Mäusen
PBS	Phosphatgepufferte Kochsalzlösung
RT	Raumtemperatur
SLE	systemischer Lupus erythematodes
Sm	Proteinantigen, benannt nach der SLE Patientin Stephanie Smith
SmD1	D1 Protein des Sm Antigens
SmD1 <sub>(83-119)</sub>	Peptid bestehend aus den Aminosäuren 83-119 des SmD1 Proteins
SSC	Side Scatter, Seitwärtsstreulicht bei der Durchflusszytometrie
TNF	Tumornekrosefaktor
ÜN	Über Nacht
UV	Ultraviolett
VCAM	Vascular Cell Adhesion Molecule (Adhäsionsmolekül)
wo	Wochen

## **8.2 Erklärung**

„Ich, Philipp Enghard, erkläre, dass ich die vorgelegte Dissertationsschrift mit dem Thema: „Charakterisierung der T-Zell Infiltration bei muriner Lupusnephritis“ selbst verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt, ohne die (unzulässige) Hilfe Dritter verfasst und auch in Teilen keine Kopien anderer Arbeiten dargestellt habe.“

Datum

Unterschrift

### 8.3 Danksagung

Mein erster Dank gilt meiner Arbeitsgruppe, allen vorweg Gabriela Riemekasten für immer vorhandene Hilfsbereitschaft, die vielen wertvollen Anregungen und Hinweise und ihrem netten Wesen jederzeit den Teamgeist hochzuhalten.

Zu großem Dank bin ich Dirk Langnickel verpflichtet, der mich vorbildlich in die Laborarbeit eingewiesen hat und dem ich fast mein gesamtes Knowhow verdanke.. Dank gilt auch Claudia Klein, Swen Langer und Tiina Humaljoki – ich bin euch allen freundschaftlich verbunden.

Dank gilt auch Prof. Falk Hiepe, der jederzeit hilfsbereit war und mir sehr gute Ratschläge gab.

Danke an Prof. Sinha für die Hilfe bei der Hb Bestimmung zur Erfolgskontrolle des Spülens der Nieren

Dank und Gruß geht auch an den T-Zell Club, an erster Stelle sind zu nennen Alexander Scheffold und Andreas Radbruch, denen ich viel Kritik und gute Tipps verdanke. Gleicher Dank gilt Rudi Manz und den anderen Arbeitsgruppenleitern, die immer ein offenes Ohr und eine gute Antwort parat hatten.

Grossen Dank auch an all die Mitwissenschaftler aus dem DRFZ: Daniel, Mark, Robert, Connie, Lydia, Kathrin, Kai, Kathrin, Bianka, Rainer, Till, Sascha, Arnhild, Gudrun, Kerstin, Frank, Thoralf und alle anderen die ich hier nicht aufgezählt habe.

Dank auch an die Labormanagerinnen Heidi Hecker-Kia, Heidi Schliemann und Tuula Geske.

Danke an Marc, Mama, Papa, Tante Ilse und Onkel Wolfgang für das Korrekturlesen.

## 8.4 Lebenslauf

- 1977 Geboren als Philipp Enghard am 05.04.1977 in Frankfurt/M-Höchst, zweiter Sohn der Eltern Dr. med. Brigitte Enghard und Armin Enghard.
- 1983 Besuch der Grundschule Kalbach in Frankfurt/M.
- 1987 Besuch des privaten Ganztagsgymnasiums Anna-Schmidt-Schule in Frankfurt/M.
- 1993/94 Besuch der 11. Klasse als Austauschschüler an der High-School Northfield in Northfield, Minnesota, USA.
- 1996 Bestehen des Abiturs mit der Note 1,7.
- 1996/97 Absolvierung des Zivildienstes als Krankenwagenfahrer/Rettungssanitäter beim Arbeiter-Samariter-Bund (ASB) in Frankfurt/M.
- 1997 Beginn des Studiums der Humanmedizin an der Freien Universität Berlin.
- 1999 Bestehen des Physicums mit der Note 1.  
Wechsel zum klinischen Studiumsabschnitt an die Charité, medizinische Fakultät der Humboldt Universität Berlin.
- 1999-2000 Repräsentant im Studentenparlament für die Liste „Kritische Medizin“.  
Teilnahme an einem Buchprojekt des deutschen Ärzteverbandes zur Erstellung eines Lehrbuchs der Inneren Medizin, Bearbeitung von Krankheitsbildern aus dem Bereich Onkologie/Immunologie.
- 2000 Seit Juli 2000 Stipendiat der Studienstiftung des deutschen Volkes.
- 2000/2001 Teilnahme am ERASMUS-Austauschprogramm. Studium an der medizinischen Fakultät der Universidade Nova in Lissabon, Portugal, für ein Jahr.
- 2001 Bestehen des ersten Abschnitts der ärztlichen Prüfung mit der Note 2.
- 2001 Seit Herbst 2001 Mitarbeit in der Arbeitsgruppe von Gabriela Riemekasten. Nehmen von zwei Freisemestern (Sommersemester 2002 und Wintersemester 2002/03) zum Vollzeitarbeiten im Labor.
- 2004 Ablegen des zweiten Staatsexamens mit den Noten schriftlich 2 und mündlich 1.
- 2004/2005 Praktisches Jahr:  
- 16 Wochen Radiologie an der Charité, Campus Virchow-Klinikum.  
- 16 Wochen Chirurgie am Hospital Universitario, Florianopolis, Brasilien.  
- 8 Wochen Innere Medizin am Mount Sinai Hospital/VA Bronx in New York, USA.  
- 8 Wochen Innere Medizin am Austin Hospital in Melbourne, Australien.
- 2005 Bestehen des dritten Abschnitts der ärztlichen Prüfung (Prüfungsfächer Innere Medizin, Chirurgie, Radiologie und Pharmakologie) mit der Note 1. Abschluss des Medizinstudiums mit der Gesamtnote 1.

## 8.5 Publikationsliste

### Publikationen:

Riemekasten, G., D. Langnickel, **P. Enghard**, R. Undeutsch, J. Humrich, F. Ebling, B. Hoher, T. Humaljoki, H. Neumayer, G.R. Burmester, B.H. Hahn, A. Radbruch, F.Hiepe. Immune tolerance to the SmD183-119 peptide postpones development of murine lupus by induction of Tr1 regulatory T cells. J of Immunol 2004;173(9):5835-42.

**Enghard, P.** G. Riemekasten. Regulatory T cells - a possible promising target in the treatment of autoimmune diseases. Z Rheumatol. 2003; 62(4):355-60.

**Enghard, P.**, J. Humrich, D. Langnickel, R. Manz, F. Hiepe, A. Radbruch, G. Riemekasten. Characterization of kidney infiltrating T cells in NZB/W lupus mice by flow cytometry. In preparation for Clin. Exp. Immunol.

**Enghard, P.**, D. Langnickel, G. Riemekasten. Cytokine balance in the NZB/W murine model of SLE. Manuskript eingereicht bei Scand. J. Immunol.

Langer, S., D. Langnickel, **P. Enghard**, R. Undeutsch, G.R. Burmester, F. Hiepe, A. Radbruch, A. Hamann, G.Riemekasten. The cytokine memory of SmD183-119-autoantigen-specific TH cells in SLE patients.. Manuskript eingereicht bei Arthritis Research and Therapy 2005.

### Posterpräsentationen/Abstrakts:

**Enghard, P.**, D. Langnickel, R. Manz, F. Hiepe, A. Radbruch, G. Riemekasten. Characterization of the kidney infiltrating T cells in the NZB/W F1 lupus model. Lupus 2004 - 7th International Congress on SLE and Related Conditions, New York.

**Enghard, P.**, D. Langnickel, R. Manz, F. Hiepe, A. Radbruch, G. Riemekasten. Characterization of the kidney infiltrating T cells in the NZB/W F1 lupus model. Poster- und Kurzvortrag, 24<sup>th</sup> European Workshop for Rheumatology Research 2004, Berlin.

**Enghard, P.**, D. Langnickel, G. Riemekasten. Cytokine imbalance in (NZB x NZW) F1 mice is associated with Autoantibody Titer and Nephritis. 24<sup>th</sup> European Workshop for Rheumatology Research 2004, Berlin.

G. Riemekasten, D. Langnickel, **P. Enghard**, A. Meine, B. Hoher, S. Krause, C. Weiß, T. Muzzolini, G.R. Burmester, F. Hiepe. Characterization of regulatory T cells after high-dose tolerance to SmD1 83-119. EULAR 2004, Berlin

G. Riemekasten, D. Langnickel, **P. Enghard**, A. Meine, B. Hoher, S. Krause, C. Weiß, T. Muzzolini, G.R. Burmester, F. Hiepe. Immune tolerance to the SmD183-119 peptide postpones development of murine lupus by regulatory T cells. EULAR 2003, Lissabon.

G. Riemekasten, D. Langnickel, **P. Enghard**, A. Meine, B. Hoher, S. Krause, C. Weiß, T. Muzzolini, G.R. Burmester, F. Hiepe. Immune tolerance to the SmD183-119 peptide postpones development of murine lupus. 66th Annual Scientific Meeting of American Congress of Rheumatology, New Orleans 2002, October

G. Riemekasten, D. Langnickel, **P. Enghard**, A. Meine, B. Hoher, S. Krause, C. Weiß, T. Muzzolini, G.R. Burmester, F. Hiepe. Immune tolerance to the SmD183-119 peptide postpones development of murine lupus. Eur. Conference on Lupus, Athen 2002, March

