

7. Literatur

1. Paulnock, D.M., Demick, K.P. & Coller, S.P. Analysis of interferon-gamma-dependent and -independent pathways of macrophage activation. *J Leukoc Biol* **67**, 677-82 (2000).
2. Snapper, C.M. & Paul, W.E. B cell stimulatory factor-1 (interleukin 4) prepares resting murine B cells to secrete IgG1 upon subsequent stimulation with bacterial lipopolysaccharide. *J Immunol* **139**, 10-7 (1987).
3. Coffman, R.L., Lebman, D.A. & Rothman, P. Mechanism and regulation of immunoglobulin isotype switching. *Adv Immunol* **54**, 229-70 (1993).
4. Murphy, K.M. & Reiner, S.L. The lineage decisions of helper T cells. *Nat Rev Immunol* **2**, 933-44 (2002).
5. Ho, I.C. & Glimcher, L.H. Transcription: tantalizing times for T cells. *Cell* **109 Suppl**, S109-20 (2002).
6. Kovalovsky, D. et al. The Th1 and Th2 cytokines IFN-gamma and IL-4 antagonize the inhibition of monocyte IL-1 receptor antagonist by glucocorticoids: involvement of IL-1. *Eur J Immunol* **28**, 2075-85 (1998).
7. Weaver, C.T., Harrington, L.E., Mangan, P.R., Gavrieli, M. & Murphy, K.M. Th17: an effector CD4 T cell lineage with regulatory T cell ties. *Immunity* **24**, 677-88 (2006).
8. Mangan, P.R. et al. Transforming growth factor-beta induces development of the T(H)17 lineage. *Nature* **441**, 231-4 (2006).
9. Veldhoen, M., Hocking, R.J., Atkins, C.J., Locksley, R.M. & Stockinger, B. TGFbeta in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells. *Immunity* **24**, 179-89 (2006).
10. Aggarwal, S., Ghilardi, N., Xie, M.H., de Sauvage, F.J. & Gurney, A.L. Interleukin-23 promotes a distinct CD4 T cell activation state characterized by the production of interleukin-17. *J Biol Chem* **278**, 1910-4 (2003).
11. Firestein, G.S. et al. A new murine CD4+ T cell subset with an unrestricted cytokine profile. *J Immunol* **143**, 518-25 (1989).
12. Kelso, A. & Gough, N.M. Coexpression of granulocyte-macrophage colony-stimulating factor, gamma interferon, and interleukins 3 and 4 is random in murine alloreactive T-lymphocyte clones. *Proc Natl Acad Sci U S A* **85**, 9189-93 (1988).
13. Chen, Y., Kuchroo, V.K., Inobe, J., Hafler, D.A. & Weiner, H.L. Regulatory T cell clones induced by oral tolerance: suppression of autoimmune encephalomyelitis. *Science* **265**, 1237-40 (1994).
14. Groux, H. et al. A CD4+ T-cell subset inhibits antigen-specific T-cell responses and prevents colitis. *Nature* **389**, 737-42 (1997).
15. 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**, 1151-64 (1995).
16. Hori, S., Nomura, T. & Sakaguchi, S. Control of regulatory T cell development by the transcription factor Foxp3. *Science* **299**, 1057-61 (2003).
17. Walker, L.S. & Abbas, A.K. The enemy within: keeping self-reactive T cells at bay in the periphery. *Nat Rev Immunol* **2**, 11-9 (2002).
18. Sakaguchi, S. Naturally arising CD4+ regulatory t cells for immunologic self-tolerance and negative control of immune responses. *Annu Rev Immunol* **22**, 531-62 (2004).

-
19. Sakaguchi, S. et al. Immunologic tolerance maintained by CD25+ CD4+ regulatory T cells: their common role in controlling autoimmunity, tumor immunity, and transplantation tolerance. *Immunol Rev* **182**, 18-32 (2001).
 20. Bach, J.F. Regulatory T cells under scrutiny. *Nat Rev Immunol* **3**, 189-98 (2003).
 21. Schweitzer, A.N. & Sharpe, A.H. Studies using antigen-presenting cells lacking expression of both B7-1 (CD80) and B7-2 (CD86) show distinct requirements for B7 molecules during priming versus restimulation of Th2 but not Th1 cytokine production. *J Immunol* **161**, 2762-71 (1998).
 22. Howland, K.C., Ausubel, L.J., London, C.A. & Abbas, A.K. The roles of CD28 and CD40 ligand in T cell activation and tolerance. *J Immunol* **164**, 4465-70 (2000).
 23. Clatza, A., Bonifaz, L.C., Vignali, D.A. & Moreno, J. CD40-induced aggregation of MHC class II and CD80 on the cell surface leads to an early enhancement in antigen presentation. *J Immunol* **171**, 6478-87 (2003).
 24. Seder, R.A., Gazzinelli, R., Sher, A. & Paul, W.E. Interleukin 12 acts directly on CD4+ T cells to enhance priming for interferon gamma production and diminishes interleukin 4 inhibition of such priming. *Proc Natl Acad Sci U S A* **90**, 10188-92 (1993).
 25. Hsieh, C.S. et al. Development of TH1 CD4+ T cells through IL-12 produced by Listeria-induced macrophages. *Science* **260**, 547-9 (1993).
 26. Swain, S.L., Weinberg, A.D., English, M. & Huston, G. IL-4 directs the development of Th2-like helper effectors. *J Immunol* **145**, 3796-806 (1990).
 27. Le Gros, G., Ben-Sasson, S.Z., Seder, R., Finkelman, F.D. & Paul, W.E. Generation of interleukin 4 (IL-4)-producing cells in vivo and in vitro: IL-2 and IL-4 are required for in vitro generation of IL-4-producing cells. *J Exp Med* **172**, 921-9 (1990).
 28. Steinman, R.M., Turley, S., Mellman, I. & Inaba, K. The induction of tolerance by dendritic cells that have captured apoptotic cells. *J Exp Med* **191**, 411-6 (2000).
 29. Roncarolo, M.G., Levings, M.K. & Traversari, C. Differentiation of T regulatory cells by immature dendritic cells. *J Exp Med* **193**, F5-9 (2001).
 30. Jonuleit, H., Schmitt, E., Steinbrink, K. & Enk, A.H. Dendritic cells as a tool to induce anergic and regulatory T cells. *Trends Immunol* **22**, 394-400 (2001).
 31. Jonuleit, H., Schmitt, E., Schuler, G., Knop, J. & Enk, A.H. Induction of interleukin 10-producing, nonproliferating CD4(+) T cells with regulatory properties by repetitive stimulation with allogeneic immature human dendritic cells. *J Exp Med* **192**, 1213-22 (2000).
 32. Grakoui, A., Donermeyer, D.L., Kanagawa, O., Murphy, K.M. & Allen, P.M. TCR-independent pathways mediate the effects of antigen dose and altered peptide ligands on Th cell polarization. *J Immunol* **162**, 1923-30 (1999).
 33. Kedl, R.M., Schaefer, B.C., Kappler, J.W. & Marrack, P. T cells down-modulate peptide-MHC complexes on APCs in vivo. *Nat Immunol* **3**, 27-32 (2002).
 34. Dutoit, V. et al. Functional avidity of tumor antigen-specific CTL recognition directly correlates with the stability of MHC/peptide multimer binding to TCR. *J Immunol* **168**, 1167-71 (2002).
 35. Rogers, P.R., Huston, G. & Swain, S.L. High antigen density and IL-2 are required for generation of CD4 effectors secreting Th1 rather than Th0 cytokines. *J Immunol* **161**, 3844-52 (1998).
 36. Pfeiffer, C. et al. Altered peptide ligands can control CD4 T lymphocyte differentiation in vivo. *J Exp Med* **181**, 1569-74 (1995).
 37. Constant, S., Pfeiffer, C., Woodard, A., Pasqualini, T. & Bottomly, K. Extent of T cell receptor ligation can determine the functional differentiation of naive CD4+ T cells. *J Exp Med* **182**, 1591-6 (1995).

38. Hosken, N.A., Shibuya, K., Heath, A.W., Murphy, K.M. & O'Garra, A. The effect of antigen dose on CD4+ T helper cell phenotype development in a T cell receptor-alpha beta-transgenic model. *J Exp Med* **182**, 1579-84 (1995).
39. Sugihara, S. et al. Autoimmune thyroiditis induced in mice depleted of particular T cell subsets. I. Requirement of Lyt-1 dull L3T4 bright normal T cells for the induction of thyroiditis. *J Immunol* **141**, 105-13 (1988).
40. La Cava, A. & Sarvetnick, N. The role of cytokines in autoimmunity. *Curr Dir Autoimmun* **1**, 56-71 (1999).
41. Liblau, R.S., Singer, S.M. & McDevitt, H.O. Th1 and Th2 CD4+ T cells in the pathogenesis of organ-specific autoimmune diseases. *Immunol Today* **16**, 34-8 (1995).
42. Mueller, R., Krahl, T. & Sarvetnick, N. Pancreatic expression of interleukin-4 abrogates insulitis and autoimmune diabetes in nonobese diabetic (NOD) mice. *J Exp Med* **184**, 1093-9 (1996).
43. Williams, K.C., Ulvestad, E. & Hickey, W.F. Immunology of multiple sclerosis. *Clin Neurosci* **2**, 229-45 (1994).
44. Falcone, M. & Bloom, B.R. A T helper cell 2 (Th2) immune response against non-self antigens modifies the cytokine profile of autoimmune T cells and protects against experimental allergic encephalomyelitis. *J Exp Med* **185**, 901-7 (1997).
45. Myers, L.K., Tang, B., Stuart, J.M. & Kang, A.H. The role of IL-4 in regulation of murine collagen-induced arthritis. *Clin Immunol* **102**, 185-91 (2002).
46. Mauri, C., Williams, R.O., Walmsley, M. & Feldmann, M. Relationship between Th1/Th2 cytokine patterns and the arthritogenic response in collagen-induced arthritis. *Eur J Immunol* **26**, 1511-8 (1996).
47. Seddon, B. & Mason, D. Regulatory T cells in the control of autoimmunity: the essential role of transforming growth factor beta and interleukin 4 in the prevention of autoimmune thyroiditis in rats by peripheral CD4(+)CD45RC- cells and CD4(+)CD8(-) thymocytes. *J Exp Med* **189**, 279-88 (1999).
48. Rivera, J. & Gilfillan, A.M. Molecular regulation of mast cell activation. *J Allergy Clin Immunol* **117**, 1214-25; quiz 1226 (2006).
49. Haas, H. et al. Early interleukin-4: its role in the switch towards a Th2 response and IgE-mediated allergy. *Int Arch Allergy Immunol* **119**, 86-94 (1999).
50. Raz, E. et al. Preferential induction of a Th1 immune response and inhibition of specific IgE antibody formation by plasmid DNA immunization. *Proc Natl Acad Sci U S A* **93**, 5141-5 (1996).
51. Bettelli, E. et al. Loss of T-bet, but not STAT1, prevents the development of experimental autoimmune encephalomyelitis. *J Exp Med* **200**, 79-87 (2004).
52. Ferber, I.A. et al. Mice with a disrupted IFN-gamma gene are susceptible to the induction of experimental autoimmune encephalomyelitis (EAE). *J Immunol* **156**, 5-7 (1996).
53. Oppmann, B. et al. Novel p19 protein engages IL-12p40 to form a cytokine, IL-23, with biological activities similar as well as distinct from IL-12. *Immunity* **13**, 715-25 (2000).
54. Murphy, C.A. et al. Divergent pro- and antiinflammatory roles for IL-23 and IL-12 in joint autoimmune inflammation. *J Exp Med* **198**, 1951-7 (2003).
55. Cua, D.J. et al. Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain. *Nature* **421**, 744-8 (2003).
56. Lubberts, E. et al. Treatment with a neutralizing anti-murine interleukin-17 antibody after the onset of collagen-induced arthritis reduces joint inflammation, cartilage destruction, and bone erosion. *Arthritis Rheum* **50**, 650-9 (2004).

57. Koenders, M.I. et al. Induction of cartilage damage by overexpression of T cell interleukin-17A in experimental arthritis in mice deficient in interleukin-1. *Arthritis Rheum* **52**, 975-83 (2005).
58. Wolff, J.A. et al. Direct gene transfer into mouse muscle in vivo. *Science* **247**, 1465-8 (1990).
59. Tang, D.C., DeVit, M. & Johnston, S.A. Genetic immunization is a simple method for eliciting an immune response. *Nature* **356**, 152-4 (1992).
60. Fynan, E.F. et al. DNA vaccines: protective immunizations by parenteral, mucosal, and gene-gun inoculations. *Proc Natl Acad Sci U S A* **90**, 11478-82 (1993).
61. Pertmer, T.M. et al. Gene gun-based nucleic acid immunization: elicitation of humoral and cytotoxic T lymphocyte responses following epidermal delivery of nanogram quantities of DNA. *Vaccine* **13**, 1427-30 (1995).
62. Porgador, A. et al. Predominant role for directly transfected dendritic cells in antigen presentation to CD8+ T cells after gene gun immunization. *J Exp Med* **188**, 1075-82 (1998).
63. Condon, C., Watkins, S.C., Celluzzi, C.M., Thompson, K. & Falo, L.D., Jr. DNA-based immunization by in vivo transfection of dendritic cells. *Nat Med* **2**, 1122-8 (1996).
64. Garg, S. et al. Genetic tagging shows increased frequency and longevity of antigen-presenting, skin-derived dendritic cells in vivo. *Nat Immunol* **4**, 907-12 (2003).
65. Corr, M., von Damm, A., Lee, D.J. & Tighe, H. In vivo priming by DNA injection occurs predominantly by antigen transfer. *J Immunol* **163**, 4721-7 (1999).
66. Bouloc, A., Walker, P., Grivel, J.C., Vogel, J.C. & Katz, S.I. Immunization through dermal delivery of protein-encoding DNA: a role for migratory dendritic cells. *Eur J Immunol* **29**, 446-54 (1999).
67. Ulmer, J.B. et al. Heterologous protection against influenza by injection of DNA encoding a viral protein. *Science* **259**, 1745-9 (1993).
68. Robinson, H.L., Hunt, L.A. & Webster, R.G. Protection against a lethal influenza virus challenge by immunization with a haemagglutinin-expressing plasmid DNA. *Vaccine* **11**, 957-60 (1993).
69. Ugen, K.E. et al. DNA vaccination with HIV-1 expressing constructs elicits immune responses in humans. *Vaccine* **16**, 1818-21 (1998).
70. Wang, R. et al. Induction of antigen-specific cytotoxic T lymphocytes in humans by a malaria DNA vaccine. *Science* **282**, 476-80 (1998).
71. Boyle, J.S., Brady, J.L. & Lew, A.M. Enhanced responses to a DNA vaccine encoding a fusion antigen that is directed to sites of immune induction. *Nature* **392**, 408-11 (1998).
72. Kim, J.J. et al. Modulation of amplitude and direction of in vivo immune responses by co-administration of cytokine gene expression cassettes with DNA immunogens. *Eur J Immunol* **28**, 1089-103 (1998).
73. Xiang, Z. & Ertl, H.C. Manipulation of the immune response to a plasmid-encoded viral antigen by coinoculation with plasmids expressing cytokines. *Immunity* **2**, 129-35 (1995).
74. Waisman, A. et al. Suppressive vaccination with DNA encoding a variable region gene of the T-cell receptor prevents autoimmune encephalomyelitis and activates Th2 immunity. *Nat Med* **2**, 899-905 (1996).
75. Kim, J.J. et al. Engineering of in vivo immune responses to DNA immunization via codelivery of costimulatory molecule genes. *Nat Biotechnol* **15**, 641-6 (1997).
76. Gurunathan, S., Wu, C.Y., Freidag, B.L. & Seder, R.A. DNA vaccines: a key for inducing long-term cellular immunity. *Curr Opin Immunol* **12**, 442-7 (2000).

77. Drew, D.R., Lightowlers, M. & Strugnell, R.A. Humoral immune responses to DNA vaccines expressing secreted, membrane bound and non-secreted forms of the *Tania ovis* 45W antigen. *Vaccine* **18**, 2522-32 (2000).
78. Ramsay, A.J. et al. Genetic vaccination strategies for enhanced cellular, humoral and mucosal immunity. *Immunol Rev* **171**, 27-44 (1999).
79. Torres, C.A., Iwasaki, A., Barber, B.H. & Robinson, H.L. Differential dependence on target site tissue for gene gun and intramuscular DNA immunizations. *J Immunol* **158**, 4529-32 (1997).
80. Pertmer, T.M., Roberts, T.R. & Haynes, J.R. Influenza virus nucleoprotein-specific immunoglobulin G subclass and cytokine responses elicited by DNA vaccination are dependent on the route of vector DNA delivery. *J Virol* **70**, 6119-25 (1996).
81. Feltquate, D.M., Heaney, S., Webster, R.G. & Robinson, H.L. Different T helper cell types and antibody isotypes generated by saline and gene gun DNA immunization. *J Immunol* **158**, 2278-84 (1997).
82. Alvarez, D. et al. Cutaneous antigen priming via gene gun leads to skin-selective Th2 immune-inflammatory responses. *J Immunol* **174**, 1664-74 (2005).
83. Oran, A.E. & Robinson, H.L. DNA vaccines, combining form of antigen and method of delivery to raise a spectrum of IFN-gamma and IL-4-producing CD4+ and CD8+ T cells. *J Immunol* **171**, 1999-2005 (2003).
84. Sato, Y. et al. Immunostimulatory DNA sequences necessary for effective intradermal gene immunization. *Science* **273**, 352-4 (1996).
85. Krieg, A.M. CpG motifs in bacterial DNA and their immune effects. *Annu Rev Immunol* **20**, 709-60 (2002).
86. Leclerc, C., Deriaud, E., Rojas, M. & Whalen, R.G. The preferential induction of a Th1 immune response by DNA-based immunization is mediated by the immunostimulatory effect of plasmid DNA. *Cell Immunol* **179**, 97-106 (1997).
87. Chow, Y.H. et al. Development of Th1 and Th2 populations and the nature of immune responses to hepatitis B virus DNA vaccines can be modulated by codelivery of various cytokine genes. *J Immunol* **160**, 1320-9 (1998).
88. Iwasaki, A., Torres, C.A., Ohashi, P.S., Robinson, H.L. & Barber, B.H. The dominant role of bone marrow-derived cells in CTL induction following plasmid DNA immunization at different sites. *J Immunol* **159**, 11-4 (1997).
89. Geissler, M., Gesien, A. & Wands, J.R. Inhibitory effects of chronic ethanol consumption on cellular immune responses to hepatitis C virus core protein are reversed by genetic immunizations augmented with cytokine-expressing plasmids. *J Immunol* **159**, 5107-13 (1997).
90. Kim, J.J. et al. In vivo engineering of a cellular immune response by coadministration of IL-12 expression vector with a DNA immunogen. *J Immunol* **158**, 816-26 (1997).
91. Garren, H. et al. Combination of gene delivery and DNA vaccination to protect from and reverse Th1 autoimmune disease via deviation to the Th2 pathway. *Immunity* **15**, 15-22 (2001).
92. Daheshia, M., Kuklin, N., Kanangat, S., Manickan, E. & Rouse, B.T. Suppression of ongoing ocular inflammatory disease by topical administration of plasmid DNA encoding IL-10. *J Immunol* **159**, 1945-52 (1997).
93. Song, E. et al. RNA interference targeting Fas protects mice from fulminant hepatitis. *Nat Med* **9**, 347-51 (2003).
94. Fire, A. et al. Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*. *Nature* **391**, 806-11 (1998).
95. Dykxhoorn, D.M., Novina, C.D. & Sharp, P.A. Killing the messenger: short RNAs that silence gene expression. *Nat Rev Mol Cell Biol* **4**, 457-67 (2003).

96. Cogoni, C. & Macino, G. Gene silencing in *Neurospora crassa* requires a protein homologous to RNA-dependent RNA polymerase. *Nature* **399**, 166-9 (1999).
97. Dalmay, T., Hamilton, A., Mueller, E. & Baulcombe, D.C. Potato virus X amplicons in *arabidopsis* mediate genetic and epigenetic gene silencing. *Plant Cell* **12**, 369-79 (2000).
98. Sijen, T. & Kooter, J.M. Post-transcriptional gene-silencing: RNAs on the attack or on the defense? *Bioessays* **22**, 520-31 (2000).
99. Elbashir, S.M. et al. Duplexes of 21-nucleotide RNAs mediate RNA interference in cultured mammalian cells. *Nature* **411**, 494-8 (2001).
100. Hammond, S.M., Bernstein, E., Beach, D. & Hannon, G.J. An RNA-directed nuclease mediates post-transcriptional gene silencing in *Drosophila* cells. *Nature* **404**, 293-6 (2000).
101. Caplen, N.J., Fleenor, J., Fire, A. & Morgan, R.A. dsRNA-mediated gene silencing in cultured *Drosophila* cells: a tissue culture model for the analysis of RNA interference. *Gene* **252**, 95-105 (2000).
102. Paddison, P.J., Caudy, A.A. & Hannon, G.J. Stable suppression of gene expression by RNAi in mammalian cells. *Proc Natl Acad Sci U S A* **99**, 1443-8 (2002).
103. Brummelkamp, T.R., Bernards, R. & Agami, R. A system for stable expression of short interfering RNAs in mammalian cells. *Science* **296**, 550-3 (2002).
104. Brummelkamp, T.R., Bernards, R. & Agami, R. Stable suppression of tumorigenicity by virus-mediated RNA interference. *Cancer Cell* **2**, 243-7 (2002).
105. Stewart, S.A. et al. Lentivirus-delivered stable gene silencing by RNAi in primary cells. *Rna* **9**, 493-501 (2003).
106. Racz, Z. & Hamar, P. Can siRNA technology provide the tools for gene therapy of the future? *Curr Med Chem* **13**, 2299-307 (2006).
107. Devi, G.R. siRNA-based approaches in cancer therapy. *Cancer Gene Ther* **13**, 819-29 (2006).
108. Rice, J., King, C.A., Spellerberg, M.B., Fairweather, N. & Stevenson, F.K. Manipulation of pathogen-derived genes to influence antigen presentation via DNA vaccines. *Vaccine* **17**, 3030-8 (1999).
109. Wu, T.C. et al. Engineering an intracellular pathway for major histocompatibility complex class II presentation of antigens. *Proc Natl Acad Sci U S A* **92**, 11671-5 (1995).
110. Tobery, T.W. & Siliciano, R.F. Targeting of HIV-1 antigens for rapid intracellular degradation enhances cytotoxic T lymphocyte (CTL) recognition and the induction of de novo CTL responses in vivo after immunization. *J Exp Med* **185**, 909-20 (1997).
111. Schiavo, R. et al. Chemokine receptor targeting efficiently directs antigens to MHC class I pathways and elicits antigen-specific CD8+ T-cell responses. *Blood* **107**, 4597-605 (2006).
112. Sudowe, S., Ludwig-Portugall, I., Montermann, E., Ross, R. & Reske-Kunz, A.B. Transcriptional targeting of dendritic cells in gene gun-mediated DNA immunization favors the induction of type 1 immune responses. *Mol Ther* **8**, 567-75 (2003).
113. Ross, R. et al. Transcriptional targeting of dendritic cells for gene therapy using the promoter of the cytoskeletal protein fascin. *Gene Ther* **10**, 1035-40 (2003).
114. Brocker, T., Riedinger, M. & Karjalainen, K. Targeted expression of major histocompatibility complex (MHC) class II molecules demonstrates that dendritic cells can induce negative but not positive selection of thymocytes in vivo. *J Exp Med* **185**, 541-50 (1997).

115. Kurts, C. et al. Constitutive class I-restricted exogenous presentation of self antigens in vivo. *J Exp Med* **184**, 923-30 (1996).
116. McCoy, K.L., Noone, M., Inman, J.K. & Stutzman, R. Exogenous antigens internalized through transferrin receptors activate CD4+ T cells. *J Immunol* **150**, 1691-704 (1993).
117. Bonehill, A. et al. Messenger RNA-electroporated dendritic cells presenting MAGE-A3 simultaneously in HLA class I and class II molecules. *J Immunol* **172**, 6649-57 (2004).
118. Rodriguez, F., Harkins, S., Redwine, J.M., de Pereda, J.M. & Whitton, J.L. CD4(+) T cells induced by a DNA vaccine: immunological consequences of epitope-specific lysosomal targeting. *J Virol* **75**, 10421-30 (2001).
119. Arruda, L.B. et al. Dendritic cell-lysosomal-associated membrane protein (LAMP) and LAMP-1-HIV-1 gag chimeras have distinct cellular trafficking pathways and prime T and B cell responses to a diverse repertoire of epitopes. *J Immunol* **177**, 2265-75 (2006).
120. Sanderson, S., Frauwirth, K. & Shastri, N. Expression of endogenous peptide-major histocompatibility complex class II complexes derived from invariant chain-antigen fusion proteins. *Proc Natl Acad Sci U S A* **92**, 7217-21 (1995).
121. Bakke, O. & Nordeng, T.W. Intracellular traffic to compartments for MHC class II peptide loading: signals for endosomal and polarized sorting. *Immunol Rev* **172**, 171-87 (1999).
122. van Bergen, J. et al. Get into the groove! Targeting antigens to MHC class II. *Immunol Rev* **172**, 87-96 (1999).
123. Nagata, T. et al. Immunization with plasmid DNA encoding MHC class II binding peptide/CLIP-replaced invariant chain (Ii) induces specific helper T cells in vivo: the assessment of Ii p31 and p41 isoforms as vehicles for immunization. *Vaccine* **20**, 105-14 (2001).
124. Toda, M. et al. DNA vaccine using invariant chain gene for delivery of CD4+ T cell epitope peptide derived from Japanese cedar pollen allergen inhibits allergen-specific IgE response. *Eur J Immunol* **32**, 1631-9 (2002).
125. Nagata, T. et al. Induction of protective immunity to *Listeria monocytogenes* by immunization with plasmid DNA expressing a helper T-cell epitope that replaces the class II-associated invariant chain peptide of the invariant chain. *Infect Immun* **70**, 2676-80 (2002).
126. Jenkins, M.K. et al. In vivo activation of antigen-specific CD4 T cells. *Annu Rev Immunol* **19**, 23-45 (2001).
127. Pape, K.A. et al. Use of adoptive transfer of T-cell-antigen-receptor-transgenic T cell for the study of T-cell activation in vivo. *Immunol Rev* **156**, 67-78 (1997).
128. Frentsche, M. et al. Direct access to CD4+ T cells specific for defined antigens according to CD154 expression. *Nat Med* **11**, 1118-24 (2005).
129. Yellin, M.J. et al. CD40 molecules induce down-modulation and endocytosis of T cell surface T cell-B cell activating molecule/CD40-L. Potential role in regulating helper effector function. *J Immunol* **152**, 598-608 (1994).
130. Hanahan, D. Studies on transformation of *Escherichia coli* with plasmids. *J Mol Biol* **166**, 557-80 (1983).
131. Miller, J. & Germain, R.N. Efficient cell surface expression of class II MHC molecules in the absence of associated invariant chain. *J Exp Med* **164**, 1478-89 (1986).
132. MacDowell EC, A.E., MacDowell CG. The prenatal growth of the mouse. *Journal of General Physiology* **11**, 57-70 (1927).

-
133. Little CC, B.H. The occurrence of four inheritable morphological variations in mice and their possible relation to treatment with x-rays. *Journal of Experimental Zoology* **41**, 45-91 (1924).
 134. Murphy, K.M., Heimberger, A.B. & Loh, D.Y. Induction by antigen of intrathymic apoptosis of CD4+CD8+TCR $\delta\gamma$ thymocytes in vivo. *Science* **250**, 1720-3 (1990).
 135. Barnden, M.J., Allison, J., Heath, W.R. & Carbone, F.R. Defective TCR expression in transgenic mice constructed using cDNA-based alpha- and beta-chain genes under the control of heterologous regulatory elements. *Immunol Cell Biol* **76**, 34-40 (1998).
 136. Chen, J. et al. Immunoglobulin gene rearrangement in B cell deficient mice generated by targeted deletion of the JH locus. *Int Immunol* **5**, 647-56 (1993).
 137. Kawai, T., Adachi, O., Ogawa, T., Takeda, K. & Akira, S. Unresponsiveness of MyD88-deficient mice to endotoxin. *Immunity* **11**, 115-22 (1999).
 138. Rogers, W.O. et al. Visualization of antigen-specific T cell activation and cytokine expression in vivo. *J Immunol* **158**, 649-57 (1997).
 139. Hochrein, H. et al. Interleukin (IL)-4 is a major regulatory cytokine governing bioactive IL-12 production by mouse and human dendritic cells. *J Exp Med* **192**, 823-33 (2000).
 140. Li, M. et al. Induction of RNA interference in dendritic cells. *Immunol Res* **30**, 215-30 (2004).
 141. Hill, J.A. et al. Immune modulation by silencing IL-12 production in dendritic cells using small interfering RNA. *J Immunol* **171**, 691-6 (2003).
 142. Borg, C. et al. NK cell activation by dendritic cells (DCs) requires the formation of a synapse leading to IL-12 polarization in DCs. *Blood* **104**, 3267-75 (2004).
 143. Raz, E. et al. Systemic immunological effects of cytokine genes injected into skeletal muscle. *Proc Natl Acad Sci U S A* **90**, 4523-7 (1993).
 144. Okada, E. et al. Intranasal immunization of a DNA vaccine with IL-12- and granulocyte-macrophage colony-stimulating factor (GM-CSF)-expressing plasmids in liposomes induces strong mucosal and cell-mediated immune responses against HIV-1 antigens. *J Immunol* **159**, 3638-47 (1997).
 145. Song, K., Chang, Y. & Prud'homme, G.J. IL-12 plasmid-enhanced DNA vaccination against carcinoembryonic antigen (CEA) studied in immune-gene knockout mice. *Gene Ther* **7**, 1527-35 (2000).
 146. Hochrein, H. et al. Differential production of IL-12, IFN-alpha, and IFN-gamma by mouse dendritic cell subsets. *J Immunol* **166**, 5448-55 (2001).
 147. Jankovic, D., Sher, A. & Yap, G. Th1/Th2 effector choice in parasitic infection: decision making by committee. *Curr Opin Immunol* **13**, 403-9 (2001).
 148. Wolfe, T. et al. Endogenous expression levels of autoantigens influence success or failure of DNA immunizations to prevent type 1 diabetes: addition of IL-4 increases safety. *Eur J Immunol* **32**, 113-21 (2002).
 149. Fallon, P.G. et al. IL-4 induces characteristic Th2 responses even in the combined absence of IL-5, IL-9, and IL-13. *Immunity* **17**, 7-17 (2002).
 150. Chatelain, R., Varkila, K. & Coffman, R.L. IL-4 induces a Th2 response in Leishmania major-infected mice. *J Immunol* **148**, 1182-7 (1992).
 151. Racke, M.K. et al. Retinoid treatment of experimental allergic encephalomyelitis. IL-4 production correlates with improved disease course. *J Immunol* **154**, 450-8 (1995).
 152. Kim, T.W. et al. Modification of professional antigen-presenting cells with small interfering RNA in vivo to enhance cancer vaccine potency. *Cancer Res* **65**, 309-16 (2005).

153. Peng, S. et al. Vaccination with dendritic cells transfected with BAK and BAX siRNA enhances antigen-specific immune responses by prolonging dendritic cell life. *Hum Gene Ther* **16**, 584-93 (2005).
154. Yang, R. et al. Papillomavirus-like particles stimulate murine bone marrow-derived dendritic cells to produce alpha interferon and Th1 immune responses via MyD88. *J Virol* **78**, 11152-60 (2004).
155. Chen, X., He, J. & Chang, L.J. Alteration of T cell immunity by lentiviral transduction of human monocyte-derived dendritic cells. *Retrovirology* **1**, 37 (2004).
156. Liu, G. et al. Small interference RNA modulation of IL-10 in human monocyte-derived dendritic cells enhances the Th1 response. *Eur J Immunol* **34**, 1680-7 (2004).
157. Szabo, S.J. et al. A novel transcription factor, T-bet, directs Th1 lineage commitment. *Cell* **100**, 655-69 (2000).
158. Weiss, R. et al. Gene gun bombardment with gold particles displays a particular Th2-promoting signal that over-rules the Th1-inducing effect of immunostimulatory CpG motifs in DNA vaccines. *Vaccine* **20**, 3148-54 (2002).
159. Gurunathan, S., Klinman, D.M. & Seder, R.A. DNA vaccines: immunology, application, and optimization*. *Annu Rev Immunol* **18**, 927-74 (2000).
160. Hemmi, H. et al. A Toll-like receptor recognizes bacterial DNA. *Nature* **408**, 740-5 (2000).
161. Wagner, H. The immunobiology of the TLR9 subfamily. *Trends Immunol* **25**, 381-6 (2004).
162. Liu, L., Zhou, X., Liu, H., Xiang, L. & Yuan, Z. CpG motif acts as a 'danger signal' and provides a T helper type 1-biased microenvironment for DNA vaccination. *Immunology* **115**, 223-30 (2005).
163. Takeda, K. & Akira, S. TLR signaling pathways. *Semin Immunol* **16**, 3-9 (2004).
164. Ishii, K.J. & Akira, S. Innate immune recognition of nucleic acids: beyond toll-like receptors. *Int J Cancer* **117**, 517-23 (2005).
165. Hacker, H. et al. Immune cell activation by bacterial CpG-DNA through myeloid differentiation marker 88 and tumor necrosis factor receptor-associated factor (TRAF)6. *J Exp Med* **192**, 595-600 (2000).
166. Takeshita, F. et al. Signal transduction pathways mediated by the interaction of CpG DNA with Toll-like receptor 9. *Semin Immunol* **16**, 17-22 (2004).
167. Spies, B. et al. Vaccination with plasmid DNA activates dendritic cells via Toll-like receptor 9 (TLR9) but functions in TLR9-deficient mice. *J Immunol* **171**, 5908-12 (2003).
168. Sugawara, I., Yamada, H., Mizuno, S., Takeda, K. & Akira, S. Mycobacterial infection in MyD88-deficient mice. *Microbiol Immunol* **47**, 841-7 (2003).
169. Scanga, C.A. et al. Cutting edge: MyD88 is required for resistance to Toxoplasma gondii infection and regulates parasite-induced IL-12 production by dendritic cells. *J Immunol* **168**, 5997-6001 (2002).
170. Takeuchi, O., Hoshino, K. & Akira, S. Cutting edge: TLR2-deficient and MyD88-deficient mice are highly susceptible to *Staphylococcus aureus* infection. *J Immunol* **165**, 5392-6 (2000).
171. Constant, S., Schweitzer, N., West, J., Ranney, P. & Bottomly, K. B lymphocytes can be competent antigen-presenting cells for priming CD4+ T cells to protein antigens in vivo. *J Immunol* **155**, 3734-41 (1995).
172. Constant, S.L. B lymphocytes as antigen-presenting cells for CD4+ T cell priming in vivo. *J Immunol* **162**, 5695-703 (1999).

173. Skok, J., Poudrier, J. & Gray, D. Dendritic cell-derived IL-12 promotes B cell induction of Th2 differentiation: a feedback regulation of Th1 development. *J Immunol* **163**, 4284-91 (1999).
174. Lauterbach, H., Gruber, A., Ried, C., Cheminay, C. & Brocker, T. Insufficient APC capacities of dendritic cells in gene gun-mediated DNA vaccination. *J Immunol* **176**, 4600-7 (2006).
175. Harris, N.L. & Ronchese, F. The role of B7 costimulation in T-cell immunity. *Immunol Cell Biol* **77**, 304-11 (1999).
176. Rogers, P.R. & Croft, M. CD28, Ox-40, LFA-1, and CD4 modulation of Th1/Th2 differentiation is directly dependent on the dose of antigen. *J Immunol* **164**, 2955-63 (2000).
177. Constant, S.L. & Bottomly, K. Induction of Th1 and Th2 CD4+ T cell responses: the alternative approaches. *Annu Rev Immunol* **15**, 297-322 (1997).
178. Malcherek, G. et al. MHC class II-associated invariant chain peptide replacement by T cell epitopes: engineered invariant chain as a vehicle for directed and enhanced MHC class II antigen processing and presentation. *Eur J Immunol* **28**, 1524-33 (1998).
179. DiMolfetto, L., Neal, H.A., Wu, A., Reilly, C. & Lo, D. The density of the class II MHC T cell receptor ligand influences IFN-gamma/IL-4 ratios in immune responses in vivo. *Cell Immunol* **183**, 70-9 (1998).
180. Carstens, C., Newman, D.K., Bohlen, H., Konig, A. & Koch, N. Invariant chains with the class II binding site replaced by a sequence from influenza virus matrix protein constrain low-affinity sequences to MHC II presentation. *Int Immunol* **12**, 1561-8 (2000).
181. Gregers, T.F. et al. MHC class II loading of high or low affinity peptides directed by Ii/peptide fusion constructs: implications for T cell activation. *Int Immunol* **15**, 1291-9 (2003).
182. van Tienhoven, E.A. et al. Induction of antigen specific CD4+ T cell responses by invariant chain based DNA vaccines. *Vaccine* **19**, 1515-9 (2001).
183. Feuerer, M., Eulenburg, K., Loddenkemper, C., Hamann, A. & Huehn, J. Self-limitation of Th1-mediated inflammation by IFN-gamma. *J Immunol* **176**, 2857-63 (2006).
184. Szczepanik, M. et al. B-1 B cells mediate required early T cell recruitment to elicit protein-induced delayed-type hypersensitivity. *J Immunol* **171**, 6225-35 (2003).

8. Anhang

Danksagung

Ein großer Dank gilt Dr. Alexander Scheffold, für die hervorragende Betreuung, die wissenschaftliche Diskussion und Ansprechbarkeit bei allen Problemen, sowie für die besondere Atmosphäre in seiner Arbeitgruppe.

Ich möchte mich bei Herrn Prof. Dr. Andreas Radbruch bedanken, für die Möglichkeit diese Arbeit am DRFZ anzufertigen und dafür, dass das DRFZ ein Institut mit einem sehr hilfsbereiten, internationalen und multikulturellen Arbeitsklima ist.

Ich bedanke mich bei Herrn Prof. Dr. Rupert Mutzel und bei Herrn Prof. Dr. Alf Hamann für die Begutachtung meiner Doktorarbeit.

Ein ganz besonderer Dank geht an alle Mitglieder sowie ehemalige Mitglieder meiner Arbeitsgruppe für die außergewöhnlich freundschaftliche und warme Arbeitsatmosphäre. Vor allem möchte ich Till Muzzolini, Frank Hardung, Maurus de la Rosa, Dennis Kirchhoff, Sascha Rutz, Heike Dorninger, Manuela Krüger, Sophie Gaubert, Marko Janke, Thordis Hohnstein, Susan Brandenburg, Andrei Mantei, Sandy Vaddakadatu und Lasse Köhler danken.

Vor allem möchte ich mich bei meinen Eltern bedanken, die mich immer unterstützt haben, immer für mich da waren und mir mein Studium ermöglichten sowie bei Ingrid Kosinski für die Korrektur dieser Arbeit und ihre emotionale Unterstützung.

Mein größter Dank geht an meinen Partner Sigi, für seine Hilfe, sein Verständnis und seine Liebe.

Erklärung

Die vorliegende Arbeit wurde von Februar 2003 bis März 2007 in der Arbeitsgruppe von Dr. Alexander Scheffold am Deutschen Rheumaforschungszentrum Berlin durchgeführt.

Hierdurch versichere ich, dass ich die vorgelegte Dissertation selbstständig und ohne unerlaubte Hilfe angefertigt habe. Alle Quellen und Hilfsmittel, die für die Anfertigung dieser Arbeit verwendet wurden, sind vollständig im Text aufgeführt.

Berlin, März 2007