

Regulatory T Cells, Th17 Effector Cells
and Cytokine Microenvironment
in Inflammatory Bowel Disease
and Coeliac Disease

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References

- Abbas, A. and Lichtman, A. (2005). Cellular and Molecular Immunology. Fifth Edition. Philadelphia, USA, Elsevier Saunders.
- Abraham, C. and Cho, J. H. (2008). IL-23 and Autoimmunity: New Insights into the Pathogenesis of Inflammatory Bowel Disease. Annu Rev Med.
- Access-Economics. (2007). "The Economic Costs of Crohn's Disease and Ulcerative Colitis. Australian Crohn's and Colitis Association.
- Acosta-Rodriguez, E. V., Napolitani, G., Lanzavecchia, A. and Sallusto, F. (2007). Interleukins 1beta and 6 but not transforming growth factor-beta are essential for the differentiation of interleukin 17-producing human T helper cells. Nat Immunol **8**(9): 942-949.
- Afzali, B., Lombardi, G., Lechler, R. I. and Lord, G. M. (2007). The role of T helper 17 (Th17) and regulatory T cells (Treg) in human organ transplantation and autoimmune disease. Clin Exp Immunol **148**(1): 32-46.
- Aggarwal, S., Ghilardi, N., Xie, M. H., de Sauvage, F. J. and Gurney, A. L. (2003). Interleukin-23 promotes a distinct CD4 T cell activation state characterized by the production of interleukin-17. J Biol Chem **278**(3): 1910-1914.
- Al-Sadi, R. M. and Ma, T. Y. (2007). IL-1beta causes an increase in intestinal epithelial tight junction permeability. J Immunol **178**(7): 4641-4649.
- Ali, T., Lam, D., Bronze, M. S. and Humphrey, M. B. (2009). Osteoporosis in inflammatory bowel disease. Am J Med **122**(7): 599-604.

Allan, S. E., Crome, S. Q., Crellin, N. K., Passerini, L., Steiner, T. S., Bacchetta, R., Roncarolo, M. G. and Levings, M. K. (2007). Activation-induced FOXP3 in human T effector cells does not suppress proliferation or cytokine production. *Int Immunol* **19**(4): 345-354.

Anderson, C. A., Massey, D. C., Barrett, J. C., Prescott, N. J., Tremelling, M., Fisher, S. A., Gwilliam, R., Jacob, J., Nimmo, E. R., Drummond, H., Lees, C. W., Onnie, C. M., Hanson, C., Blaszczyk, K., Ravindrarajah, R., Hunt, S., Varma, D., Hammond, N., Lewis, G., Attlesey, H., Watkins, N., Ouwehand, W., Strachan, D., McArdle, W., Lewis, C. M., Lobo, A., Sanderson, J., Jewell, D. P., Deloukas, P., Mansfield, J. C., Mathew, C. G., Satsangi, J. and Parkes, M. (2009). Investigation of Crohn's disease risk Loci in ulcerative colitis further defines their molecular relationship. *Gastroenterology* **136**(2): 523-529 e523.

Anderson, R. P., Degano, P., Godkin, A. J., Jewell, D. P. and Hill, A. V. (2000). In vivo antigen challenge in celiac disease identifies a single transglutaminase-modified peptide as the dominant A-gliadin T-cell epitope. *Nat Med* **6**(3): 337-342.

Anderson, S. J. and Coleclough, C. (1993). Regulation of CD4 and CD8 expression on mouse T cells. Active removal from the cell surface by two mechanisms. *J Immunol* **151**(10): 5123-5134.

Annunziato, F., Cosmi, L., Liotta, F., Maggi, E. and Romagnani, S. (2008). The phenotype of human Th17 cells and their precursors, the cytokines that mediate their differentiation and the role of Th17 cells in inflammation. *Int Immunol* **20**(11): 1361-1368.

- Annunziato, F., Cosmi, L., Santarlasci, V., Maggi, L., Liotta, F., Mazzinghi, B., Parente, E., Fili, L., Ferri, S., Frosali, F., Giudici, F., Romagnani, P., Parronchi, P., Tonelli, F., Maggi, E. and Romagnani, S. (2007). Phenotypic and functional features of human Th17 cells. *J Exp Med* **204**(8): 1849-1861.
- Ansel, K. M., Lee, D. U. and Rao, A. (2003). An epigenetic view of helper T cell differentiation. *Nat Immunol* **4**(7): 616-623.
- Arend, W. P. (2002). The balance between IL-1 and IL-1Ra in disease. *Cytokine Growth Factor Rev* **13**(4-5): 323-340.
- Arend, W. P., Palmer, G. and Gabay, C. (2008). IL-1, IL-18, and IL-33 families of cytokines. *Immunol Rev* **223**: 20-38.
- Arora, S. K. (2002). Analysis of intracellular cytokines using flowcytometry. *Methods Cell Sci* **24**(1-3): 37-40.
- Arya, M., Shergill, I. S., Williamson, M., Gommersall, L., Arya, N. and Patel, H. R. (2005). Basic principles of real-time quantitative PCR. *Expert Rev Mol Diagn* **5**(2): 209-219.
- Asakura, H., Suzuki, K. and Honma, T. (2007). Recent advances in basic and clinical aspects of inflammatory bowel disease: which steps in the mucosal inflammation should we block for the treatment of inflammatory bowel disease? *World J Gastroenterol* **13**(15): 2145-2149.
- Asakura, H., Suzuki, K., Kitahora, T. and Morizane, T. (2008). Is there a link between food and intestinal microbes and the occurrence of Crohn's disease and ulcerative colitis? *J Gastroenterol Hepatol* **23**(12): 1794-1801.

- Asakura, K., Nishiwaki, Y., Inoue, N., Hibi, T., Watanabe, M. and Takebayashi, T. (2009). Prevalence of ulcerative colitis and Crohn's disease in Japan. J Gastroenterol **44**(7): 659-665.
- Atarashi, K., Nishimura, J., Shima, T., Umesaki, Y., Yamamoto, M., Onoue, M., Yagita, H., Ishii, N., Evans, R., Honda, K. and Takeda, K. (2008). ATP drives lamina propria T(H)17 cell differentiation. Nature **455**(7214): 808-812.
- Atreya, R., Mudter, J., Finotto, S., Mullberg, J., Jostock, T., Wirtz, S., Schutz, M., Bartsch, B., Holtmann, M., Becker, C., Strand, D., Czaja, J., Schlaak, J. F., Lehr, H. A., Autschbach, F., Schurmann, G., Nishimoto, N., Yoshizaki, K., Ito, H., Kishimoto, T., Galle, P. R., Rose-John, S. and Neurath, M. F. (2000). Blockade of interleukin 6 trans signaling suppresses T-cell resistance against apoptosis in chronic intestinal inflammation: evidence in Crohn's disease and experimental colitis in vivo. Nat Med **6**(5): 583-588.
- Baecher-Allan, C., Brown, J. A., Freeman, G. J. and Hafler, D. A. (2001). CD4+CD25high regulatory cells in human peripheral blood. J Immunol **167**(3): 1245-1253.
- Baecher-Allan, C., Viglietta, V. and Hafler, D. A. (2004). Human CD4+CD25+ regulatory T cells. Semin Immunol **16**(2): 89-98.
- Baecher-Allan, C., Wolf, E. and Hafler, D. A. (2005). Functional analysis of highly defined, FACS-isolated populations of human regulatory CD4+ CD25+ T cells. Clin Immunol **115**(1): 10-18.

Banchereau, J., Briere, F., Caux, C., Davoust, J., Lebecque, S., Liu, Y. J., Pulendran, B. and Palucka, K. (2000). Immunobiology of dendritic cells. Annu Rev Immunol **18**: 767-811.

Baran, J., Kowalczyk, D., Ozog, M. and Zembala, M. (2001). Three-color flow cytometry detection of intracellular cytokines in peripheral blood mononuclear cells: comparative analysis of phorbol myristate acetate-ionomycin and phytohemagglutinin stimulation. Clin Diagn Lab Immunol **8**(2): 303-313.

Barksby, H. E., Lea, S. R., Preshaw, P. M. and Taylor, J. J. (2007). The expanding family of interleukin-1 cytokines and their role in destructive inflammatory disorders. Clin Exp Immunol **149**(2): 217-225.

Baumgart, D. C. and Carding, S. R. (2007). Inflammatory bowel disease: cause and immunobiology. Lancet **369**(9573): 1627-1640.

Bayless, T. M., Talamini, M., Kaufman, H., Norwitz, L. and Kalloo, A. (2008). "Introduction to Inflammatory Bowel Disease." Retrieved January 20, 2009, from <http://www.hopkins-gi.org/>.

Becker, C., Fantini, M. C., Wirtz, S., Nikolaev, A., Lehr, H. A., Galle, P. R., Rose-John, S. and Neurath, M. F. (2005). IL-6 signaling promotes tumor growth in colorectal cancer. Cell Cycle **4**(2): 217-220.

Beckett, C. G., Dell'Olio, D., Shidrawi, R. G., Rosen-Bronson, S. and Ciclitira, P. J. (1999). Gluten-induced nitric oxide and pro-inflammatory cytokine release by cultured coeliac small intestinal biopsies. Eur J Gastroenterol Hepatol **11**(5): 529-535.

- Benahmed, M., Meresse, B., Arnulf, B., Barbe, U., Mention, J. J., Verkarre, V., Allez, M., Cellier, C., Hermine, O. and Cerf-Bensussan, N. (2007). Inhibition of TGF-beta signaling by IL-15: a new role for IL-15 in the loss of immune homeostasis in celiac disease. *Gastroenterology* **132**(3): 994-1008.
- Bennett, C. L., Christie, J., Ramsdell, F., Brunkow, M. E., Ferguson, P. J., Whitesell, L., Kelly, T. E., Saulsbury, F. T., Chance, P. F. and Ochs, H. D. (2001). The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. *Nat Genet* **27**(1): 20-21.
- Benno, Y., Endo, K., Miyoshi, H., Okuda, T., Koishi, H. and Mitsuoka, T. (1989). Effect of rice fiber on human fecal microflora. *Microbiol Immunol* **33**(5): 435-440.
- Benno, Y., Endo, K., Mizutani, T., Namba, Y., Komori, T. and Mitsuoka, T. (1989). Comparison of fecal microflora of elderly persons in rural and urban areas of Japan. *Appl Environ Microbiol* **55**(5): 1100-1105.
- Beriou, G., Costantino, C. M., Ashley, C. W., Yang, L., Kuchroo, V. K., Baecher-Allan, C. and Hafler, D. A. (2009). IL-17 producing human peripheral regulatory T cells retain suppressive function. *Blood*.
- Bernardo, D., Garrote, J. A., Allegretti, Y., Leon, A., Gomez, E., Bermejo-Martin, J. F., Calvo, C., Riestra, S., Fernandez-Salazar, L., Blanco-Quiros, A., Chirdo, F. and Arranz, E. (2008). Higher constitutive IL15R alpha expression and lower IL-15 response threshold in coeliac disease patients. *Clin Exp Immunol* **154**(1): 64-73.
- Bernstein, C. N. and Shanahan, F. (2008). Disorders of a modern lifestyle-reconciling the epidemiology of inflammatory bowel diseases. *Gut* **57**(9): 1185-1191.

- Bethune, M. T. and Khosla, C. (2008). Parallels between pathogens and gluten peptides in celiac sprue. *PLoS Pathog* **4**(2): e34.
- Bettelli, E., Carrier, Y., Gao, W., Korn, T., Strom, T. B., Oukka, M., Weiner, H. L. and Kuchroo, V. K. (2006). Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. *Nature* **441**(7090): 235-238.
- Bettelli, E., Oukka, M. and Kuchroo, V. K. (2007). T(H)-17 cells in the circle of immunity and autoimmunity. *Nat Immunol* **8**(4): 345-350.
- Beyer, M. and Schultze, J. L. (2006). Regulatory T cells in cancer. *Blood* **108**(3): 804-811.
- Bilsborough, J. and Viney, J. L. (2004). Gastrointestinal dendritic cells play a role in immunity, tolerance, and disease. *Gastroenterology* **127**(1): 300-309.
- Blanco, P., Palucka, A. K., Pascual, V. and Banchereau, J. (2008). Dendritic cells and cytokines in human inflammatory and autoimmune diseases. *Cytokine Growth Factor Rev* **19**(1): 41-52.
- Boissier, M. C., Assier, E., Falgarone, G. and Bessis, N. (2008). Shifting the imbalance from Th1/Th2 to Th17/treg: the changing rheumatoid arthritis paradigm. *Joint Bone Spine* **75**(4): 373-375.
- Boniface, K., Blom, B., Liu, Y. J. and de Waal Malefyt, R. (2008). From interleukin-23 to T-helper 17 cells: human T-helper cell differentiation revisited. *Immunol Rev* **226**: 132-146.
- Bousvaros, A., Zurakowski, D., Duggan, C., Law, T., Rifai, N., Goldberg, N. E. and Leichtner, A. M. (1998). Vitamins A and E serum levels in children and young adults

with inflammatory bowel disease: effect of disease activity. J Pediatr Gastroenterol Nutr **26**(2): 129-135.

Braitch, M., Harikrishnan, S., Robins, R. A., Nichols, C., Fahey, A. J., Showe, L. and Constantinescu, C. S. (2009). Glucocorticoids increase CD4CD25 cell percentage and Foxp3 expression in patients with multiple sclerosis. Acta Neurol Scand **119**(4): 239-245.

Brandtzaeg, P. (2006). The changing immunological paradigm in coeliac disease. Immunol Lett **105**(2): 127-139.

Brant, S. R. (2009). Exposed: the genetic underpinnings of ulcerative colitis relative to Crohn's disease. Gastroenterology **136**(2): 396-399.

Brown, K. A., Back, S. J., Ruchelli, E. D., Markowitz, J., Mascarenhas, M., Verma, R., Piccoli, D. A. and Baldassano, R. N. (2002). Lamina propria and circulating interleukin-6 in newly diagnosed pediatric inflammatory bowel disease patients. Am J Gastroenterol **97**(10): 2603-2608.

Bruder, D., Probst-Kepper, M., Westendorf, A. M., Geffers, R., Beissert, S., Loser, K., von Boehmer, H., Buer, J. and Hansen, W. (2004). Neuropilin-1: a surface marker of regulatory T cells. Eur J Immunol **34**(3): 623-630.

Brunkow, M. E., Jeffery, E. W., Hjerrild, K. A., Paepke, B., Clark, L. B., Yasayko, S. A., Wilkinson, J. E., Galas, D., Ziegler, S. F. and Ramsdell, F. (2001). Disruption of a new forkhead/winged-helix protein, scurfin, results in the fatal lymphoproliferative disorder of the scurfy mouse. Nat Genet **27**(1): 68-73.

- Bullens, D. M., Tryoen, E., Coteur, L., Dilissen, E., Hellings, P. W., Dupont, L. J. and Ceuppens, J. L. (2006). IL-17 mRNA in sputum of asthmatic patients: linking T cell driven inflammation and granulocytic influx? *Respir Res* **7**: 135.
- Buning, J., Homann, N., von Smolinski, D., Borcherding, F., Noack, F., Stolte, M., Kohl, M., Lehnert, H. and Ludwig, D. (2008). Helminths as Governors of Inflammatory Bowel Disease. *Gut* **57**(8): 1182-1183.
- Burkitt, H. G., Young, B. and Heath, J.W. (1993). *Wheater's Functional Histology: A Text Book and Color Atlas*. New York, USA, Churchill Livingstone.
- Campbell, J. D., Cook, G., Robertson, S. E., Fraser, A., Boyd, K. S., Gracie, J. A. and Franklin, I. M. (2001). Suppression of IL-2-induced T cell proliferation and phosphorylation of STAT3 and STAT5 by tumor-derived TGF beta is reversed by IL-15. *J Immunol* **167**(1): 553-561.
- Cantorna, M. T., Nashold, F. E. and Hayes, C. E. (1994). In vitamin A deficiency multiple mechanisms establish a regulatory T helper cell imbalance with excess Th1 and insufficient Th2 function. *J Immunol* **152**(4): 1515-1522.
- Cao, D., Borjesson, O., Larsson, P., Rudin, A., Gunnarsson, I., Klareskog, L., Malmstrom, V. and Trollmo, C. (2006). FOXP3 identifies regulatory CD25bright CD4+ T cells in rheumatic joints. *Scand J Immunol* **63**(6): 444-452.
- Cao, D., Malmstrom, V., Baecher-Allan, C., Hafler, D., Klareskog, L. and Trollmo, C. (2003). Isolation and functional characterization of regulatory CD25brightCD4+ T cells from the target organ of patients with rheumatoid arthritis. *Eur J Immunol* **33**(1): 215-223.

- Cao, D., van Vollenhoven, R., Klareskog, L., Trollmo, C. and Malmstrom, V. (2004). CD25brightCD4+ regulatory T cells are enriched in inflamed joints of patients with chronic rheumatic disease. *Arthritis Res Ther* **6**(4): R335-346.
- Cataldo, F. and Montalto, G. (2007). Celiac disease in the developing countries: a new and challenging public health problem. *World J Gastroenterol* **13**(15): 2153-2159.
- Cederbom, L., Hall, H. and Ivars, F. (2000). CD4+CD25+ regulatory T cells down-regulate co-stimulatory molecules on antigen-presenting cells. *Eur J Immunol* **30**(6): 1538-1543.
- Chabaud, M., Garnero, P., Dayer, J. M., Guerne, P. A., Fossiez, F. and Miossec, P. (2000). Contribution of interleukin 17 to synovium matrix destruction in rheumatoid arthritis. *Cytokine* **12**(7): 1092-1099.
- Chehade, M. and Mayer, L. (2005). Oral tolerance and its relation to food hypersensitivities. *J Allergy Clin Immunol* **115**(1): 3-12; quiz 13.
- Chen, W., Jin, W., Hardegen, N., Lei, K. J., Li, L., Marinos, N., McGrady, G. and Wahl, S. M. (2003). Conversion of peripheral CD4+CD25- naive T cells to CD4+CD25+ regulatory T cells by TGF-beta induction of transcription factor Foxp3. *J Exp Med* **198**(12): 1875-1886.
- Chen, Y., Langrish, C. L., McKenzie, B., Joyce-Shaikh, B., Stumhofer, J. S., McClanahan, T., Blumenschein, W., Churakovsa, T., Low, J., Presta, L., Hunter, C. A., Kastlein, R. A. and Cua, D. J. (2006). Anti-IL-23 therapy inhibits multiple inflammatory pathways and ameliorates autoimmune encephalomyelitis. *J Clin Invest* **116**(5): 1317-1326.

- Chen, Z., Tato, C. M., Muul, L., Laurence, A. and O'Shea J, J. (2007). Distinct regulation of interleukin-17 in human T helper lymphocytes. *Arthritis Rheum* **56**(9): 2936-2946.
- Cheng, X., Yu, X., Ding, Y. J., Fu, Q. Q., Xie, J. J., Tang, T. T., Yao, R., Chen, Y. and Liao, Y. H. (2008). The Th17/Treg imbalance in patients with acute coronary syndrome. *Clin Immunol* **127**(1): 89-97.
- Cherbut, C., Michel, C. and Lecannu, G. (2003). The prebiotic characteristics of fructooligosaccharides are necessary for reduction of TNBS-induced colitis in rats. *J Nutr* **133**(1): 21-27.
- Chichlowski, M. and Hale, L. P. (2008). Bacterial-mucosal interactions in inflammatory bowel disease: an alliance gone bad. *Am J Physiol Gastrointest Liver Physiol* **295**(6): G1139-1149.
- Cho, J. H. (2008). The genetics and immunopathogenesis of inflammatory bowel disease. *Nat Rev Immunol* **8**(6): 458-466.
- Chtanova, T., Tangye, S. G., Newton, R., Frank, N., Hodge, M. R., Rolph, M. S. and Mackay, C. R. (2004). T follicular helper cells express a distinctive transcriptional profile, reflecting their role as non-Th1/Th2 effector cells that provide help for B cells. *J Immunol* **173**(1): 68-78.
- Church, L. D., Cook, G. P. and McDermott, M. F. (2008). Primer: inflammasomes and interleukin 1beta in inflammatory disorders. *Nat Clin Pract Rheumatol* **4**(1): 34-42.
- Ciccocioppo, R., Di Sabatino, A. and Corazza, G. R. (2005). The immune recognition of gluten in coeliac disease. *Clin Exp Immunol* **140**(3): 408-416.

- Clayburgh, D. R., Shen, L. and Turner, J. R. (2004). A porous defense: the leaky epithelial barrier in intestinal disease. *Lab Invest* **84**(3): 282-291.
- Cobbold, S. P. (2008). Regulatory T cells and transplantation tolerance. *J Nephrol* **21**(4): 485-496.
- Coffer, P. J. and Burgering, B. M. (2004). Forkhead-box transcription factors and their role in the immune system. *Nat Rev Immunol* **4**(11): 889-899.
- Coombes, J. L., Siddiqui, K. R., Arancibia-Carcamo, C. V., Hall, J., Sun, C. M., Belkaid, Y. and Powrie, F. (2007). A functionally specialized population of mucosal CD103+ DCs induces Foxp3+ regulatory T cells via a TGF-beta and retinoic acid-dependent mechanism. *J Exp Med* **204**(8): 1757-1764.
- Coquet, J. M., Chakravarti, S., Smyth, M. J. and Godfrey, D. I. (2008). Cutting edge: IL-21 is not essential for Th17 differentiation or experimental autoimmune encephalomyelitis. *J Immunol* **180**(11): 7097-7101.
- Cornish, J. A., Tan, E., Simillis, C., Clark, S. K., Teare, J. and Tekkis, P. P. (2008). The risk of oral contraceptives in the etiology of inflammatory bowel disease: a meta-analysis. *Am J Gastroenterol* **103**(9): 2394-2400.
- Corthay, A. (2006). A three-cell model for activation of naive T helper cells. *Scand J Immunol* **64**(2): 93-96.
- Cotran, R. S., Kumar, V. and Collins, T. (1999). *Robbins Pathologic Basis of Disease* (6th edition). USA, W.B. Saunders Company.
- Cottone, M., Scimeca, D., Mocciaro, F., Civitavecchia, G., Perricone, G. and Orlando, A. (2008). Clinical course of ulcerative colitis. *Dig Liver Dis* **40 Suppl 2**: S247-252.

- Crane, I. J. and Forrester, J. V. (2005). Th1 and Th2 lymphocytes in autoimmune disease. Crit Rev Immunol **25**(2): 75-102.
- Cua, D. J. and Kastelein, R. A. (2006). TGF-beta, a 'double agent' in the immune pathology war. Nat Immunol **7**(6): 557-559.
- Cua, D. J., Sherlock, J., Chen, Y., Murphy, C. A., Joyce, B., Seymour, B., Lucian, L., To, W., Kwan, S., Churakova, T., Zurawski, S., Wiekowski, M., Lira, S. A., Gorman, D., Kastelein, R. A. and Sedgwick, J. D. (2003). Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain. Nature **421**(6924): 744-748.
- Cummings, J. R., Ahmad, T., Geremia, A., Beckly, J., Cooney, R., Hancock, L., Pathan, S., Guo, C., Cardon, L. R. and Jewell, D. P. (2007). Contribution of the novel inflammatory bowel disease gene IL23R to disease susceptibility and phenotype. Inflamm Bowel Dis **13**(9): 1063-1068.
- Daculsi, R., Vaillier, D., Carron, J. C. and Gualde, N. (1998). Effect of PGE2 on the cell surface molecule expression in PMA treated thymocytes. Immunol Lett **60**(2-3): 81-88.
- de Jong, E. C., Vieira, P. L., Kalinski, P., Schuitemaker, J. H., Tanaka, Y., Wierenga, E. A., Yazdanbakhsh, M. and Kapsenberg, M. L. (2002). Microbial compounds selectively induce Th1 cell-promoting or Th2 cell-promoting dendritic cells in vitro with diverse th cell-polarizing signals. J Immunol **168**(4): 1704-1709.
- de Kleer, I. M., Wedderburn, L. R., Taams, L. S., Patel, A., Varsani, H., Klein, M., de Jager, W., Pugayung, G., Giannoni, F., Rijkers, G., Albani, S., Kuis, W. and Prakken, B. (2004). CD4+CD25bright regulatory T cells actively regulate inflammation in the

joints of patients with the remitting form of juvenile idiopathic arthritis. J Immunol **172**(10): 6435-6443.

Del Zotto, B., Mumolo, G., Pronio, A. M., Montesani, C., Tersigni, R. and Boirivant, M. (2003). TGF-beta1 production in inflammatory bowel disease: differing production patterns in Crohn's disease and ulcerative colitis. Clin Exp Immunol **134**(1): 120-126.

Desgeorges, A., Gabay, C., Silacci, P., Novick, D., Roux-Lombard, P., Grau, G., Dayer, J. M., Vischer, T. and Guerne, P. A. (1997). Concentrations and origins of soluble interleukin 6 receptor-alpha in serum and synovial fluid. J Rheumatol **24**(8): 1510-1516.

Dionne, S., Hiscott, J., D'Agata, I., Duhaime, A. and Seidman, E. G. (1997). Quantitative PCR analysis of TNF-alpha and IL-1 beta mRNA levels in pediatric IBD mucosal biopsies. Dig Dis Sci **42**(7): 1557-1566.

Domenech, E. (2006). Inflammatory bowel disease: current therapeutic options. Digestion **73 Suppl 1**: 67-76.

Dominitzki, S., Fantini, M. C., Neufert, C., Nikolaev, A., Galle, P. R., Scheller, J., Monteleone, G., Rose-John, S., Neurath, M. F. and Becker, C. (2007). Cutting edge: trans-signaling via the soluble IL-6R abrogates the induction of FoxP3 in naive CD4+CD25 T cells. J Immunol **179**(4): 2041-2045.

Dubois, B., Goubier, A., Joubert, G. and Kaiserlian, D. (2005). Oral tolerance and regulation of mucosal immunity. Cell Mol Life Sci **62**(12): 1322-1332.

Dubois, P. C. and van Heel, D. A. (2008). Translational mini-review series on the immunogenetics of gut disease: immunogenetics of coeliac disease. Clin Exp Immunol **153**(2): 162-173.

- Duchmann, R., Kaiser, I., Hermann, E., Mayet, W., Ewe, K. and Meyer zum Buschenfelde, K. H. (1995). Tolerance exists towards resident intestinal flora but is broken in active inflammatory bowel disease (IBD). Clin Exp Immunol **102**(3): 448-455.
- Duerr, R. H., Taylor, K. D., Brant, S. R., Rioux, J. D., Silverberg, M. S., Daly, M. J., Steinhart, A. H., Abraham, C., Regueiro, M., Griffiths, A., Dassopoulos, T., Bitton, A., Yang, H., Targan, S., Datta, L. W., Kistner, E. O., Schumm, L. P., Lee, A. T., Gregersen, P. K., Barmada, M. M., Rotter, J. I., Nicolae, D. L. and Cho, J. H. (2006). A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. Science **314**(5804): 1461-1463.
- Eberl, G. and Littman, D. R. (2004). Thymic origin of intestinal alphabeta T cells revealed by fate mapping of RORgammat+ cells. Science **305**(5681): 248-251.
- Elias, K. M., Laurence, A., Davidson, T. S., Stephens, G., Kanno, Y., Shevach, E. M. and O'Shea, J. J. (2008). Retinoic acid inhibits Th17 polarization and enhances FoxP3 expression through a Stat-3/Stat-5 independent signaling pathway. Blood **111**(3): 1013-1020.
- Elson, C. O., Cong, Y., Weaver, C. T., Schoeb, T. R., McClanahan, T. K., Fick, R. B. and Kastelein, R. A. (2007). Monoclonal anti-interleukin 23 reverses active colitis in a T cell-mediated model in mice. Gastroenterology **132**(7): 2359-2370.
- Emery, P., Keystone, E., Tony, H. P., Cantagrel, A., van Vollenhoven, R., Sanchez, A., Alecock, E., Lee, J. and Kremer, J. (2008). IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-

tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis **67**(11): 1516-1523.

Ersoy, O., Akin, E., Ugras, S., Buyukasik, S., Selvi, E. and Guney, G. (2009). Capsule endoscopy findings in celiac disease. Dig Dis Sci **54**(4): 825-829.

Falini, M. L., Elli, L., Caramanico, R., Bardella, M. T., Terrani, C., Roncoroni, L., Doneda, L. and Forlani, F. (2008). Immunoreactivity of antibodies against transglutaminase-deamidated gliadins in adult celiac disease. Dig Dis Sci **53**(10): 2697-2701.

Fantini, M. C., Monteleone, G. and Macdonald, T. T. (2007). New players in the cytokine orchestra of inflammatory bowel disease. Inflamm Bowel Dis **13**(11): 1419-1423.

Fantini, M. C., Rizzo, A., Fina, D., Caruso, R., Becker, C., Neurath, M. F., Macdonald, T. T., Pallone, F. and Monteleone, G. (2007). IL-21 regulates experimental colitis by modulating the balance between Treg and Th17 cells. Eur J Immunol **37**(11): 3155-3163.

Fattorossi, A., Battaglia, A., Buzzonetti, A., Ciaraffa, F., Scambia, G. and Evoli, A. (2005). Circulating and thymic CD4 CD25 T regulatory cells in myasthenia gravis: effect of immunosuppressive treatment. Immunology **116**(1): 134-141.

Feeney, M. A., Murphy, F., Clegg, A. J., Trebble, T. M., Sharer, N. M. and Snook, J. A. (2002). A case-control study of childhood environmental risk factors for the development of inflammatory bowel disease. Eur J Gastroenterol Hepatol **14**(5): 529-534.

- Fehervari, Z. and Sakaguchi, S. (2004). Development and function of CD25+CD4+ regulatory T cells. *Curr Opin Immunol* **16**(2): 203-208.
- Ferranti, P., Mamone, G., Picariello, G. and Addeo, F. (2007). Mass spectrometry analysis of gliadins in celiac disease. *J Mass Spectrom* **42**(12): 1531-1548.
- Ferwerda, G., Kramer, M., de Jong, D., Piccini, A., Joosten, L. A., Devesaginer, I., Girardin, S. E., Adema, G. J., van der Meer, J. W., Kullberg, B. J., Rubartelli, A. and Netea, M. G. (2008). Engagement of NOD2 has a dual effect on proIL-1beta mRNA transcription and secretion of bioactive IL-1beta. *Eur J Immunol* **38**(1): 184-191.
- Fina, D., Sarra, M., Caruso, R., Del Vecchio Blanco, G., Pallone, F., MacDonald, T. T. and Monteleone, G. (2008). Interleukin 21 contributes to the mucosal T helper cell type 1 response in coeliac disease. *Gut* **57**(7): 887-892.
- Fina, D., Sarra, M., Fantini, M. C., Rizzo, A., Caruso, R., Caprioli, F., Stolfi, C., Cardolini, I., Dottori, M., Boirivant, M., Pallone, F., Macdonald, T. T. and Monteleone, G. (2008). Regulation of gut inflammation and th17 cell response by interleukin-21. *Gastroenterology* **134**(4): 1038-1048.
- Fiocchi, C. (2005). Inflammatory bowel disease pathogenesis: therapeutic implications. *Chin J Dig Dis* **6**(1): 6-9.
- Firestein, G. S., Alvaro-Gracia, J. M. and Maki, R. (1990). Quantitative analysis of cytokine gene expression in rheumatoid arthritis. *J Immunol* **144**(9): 3347-3353.
- Firouzi, F., Bahari, A., Aghazadeh, R. and Zali, M. R. (2006). Appendectomy, tonsillectomy, and risk of inflammatory bowel disease: a case control study in Iran. *Int J Colorectal Dis* **21**(2): 155-159.

- Fontenot, J. D., Gavin, M. A. and Rudensky, A. Y. (2003). Foxp3 programs the development and function of CD4+CD25+ regulatory T cells. *Nat Immunol* **4**(4): 330-336.
- Fontenot, J. D., Rasmussen, J. P., Gavin, M. A. and Rudensky, A. Y. (2005). A function for interleukin 2 in Foxp3-expressing regulatory T cells. *Nat Immunol* **6**(11): 1142-1151.
- Fontenot, J. D., Rasmussen, J. P., Williams, L. M., Dooley, J. L., Farr, A. G. and Rudensky, A. Y. (2005). Regulatory T cell lineage specification by the forkhead transcription factor foxp3. *Immunity* **22**(3): 329-341.
- Fontenot, J. D. and Rudensky, A. Y. (2004). Molecular aspects of regulatory T cell development. *Semin Immunol* **16**(2): 73-80.
- Fornari, M. C., Pedreira, S., Niveloni, S., Gonzalez, D., Diez, R. A., Vazquez, H., Mazure, R., Sugai, E., Smecuol, E., Boerr, L., Maurino, E. and Bai, J. C. (1998). Pre- and post-treatment serum levels of cytokines IL-1 β , IL-6, and IL-1 receptor antagonist in celiac disease. Are they related to the associated osteopenia? *Am J Gastroenterol* **93**(3): 413-418.
- Forrest, K., Symmons, D. and Foster, P. (2004). Systematic review: is ingestion of paracetamol or non-steroidal anti-inflammatory drugs associated with exacerbations of inflammatory bowel disease? *Aliment Pharmacol Ther* **20**(10): 1035-1043.
- Foster, B., Prussin, C., Liu, F., Whitmire, J. K. and Whitton, J. L. (2007). Detection of intracellular cytokines by flow cytometry. *Curr Protoc Immunol Chapter 6*: Unit 6 24.

- Fraser, J. S. and Ciclitira, P. J. (2001). Pathogenesis of coeliac disease: implications for treatment. World J Gastroenterol **7**(6): 772-776.
- Freeman, H. J. (2008). Refractory celiac disease and sprue-like intestinal disease. World J Gastroenterol **14**(6): 828-830.
- Frisullo, G., Nociti, V., Iorio, R., Patanella, A. K., Marti, A., Assunta, B., Plantone, D., Cammarota, G., Tonali, P. A. and Batocchi, A. P. (2009). Increased CD4+CD25+Foxp3+ T cells in peripheral blood of celiac disease patients: correlation with dietary treatment. Hum Immunol **70**(6): 430-435.
- Fu, S., Zhang, N., Yopp, A. C., Chen, D., Mao, M., Chen, D., Zhang, H., Ding, Y. and Bromberg, J. S. (2004). TGF-beta induces Foxp3 + T-regulatory cells from CD4 + CD25 - precursors. Am J Transplant **4**(10): 1614-1627.
- Fujino, S., Andoh, A., Bamba, S., Ogawa, A., Hata, K., Araki, Y., Bamba, T. and Fujiyama, Y. (2003). Increased expression of interleukin 17 in inflammatory bowel disease. Gut **52**(1): 65-70.
- Fukushima, K., West, G. and Fiocchi, C. (1995). Adequacy of mucosal biopsies for evaluation of intestinal cytokine-specific mRNA. Comparative study of RT-PCR in biopsies and isolated cells from normal and inflamed intestine. Dig Dis Sci **40**(7): 1498-1505.
- Furihata, M., Sawada, T., Okada, T., Ishizuka, M., Horie, T., Takagi, K., Nagata, H. and Kubota, K. (2006). Total colectomy improves altered distribution of regulatory T cells in patients with ulcerative colitis. World J Surg **30**(4): 590-597.

- Fuss, I. J., Heller, F., Boirivant, M., Leon, F., Yoshida, M., Fichtner-Feigl, S., Yang, Z., Exley, M., Kitani, A., Blumberg, R. S., Mannon, P. and Strober, W. (2004). Nonclassical CD1d-restricted NK T cells that produce IL-13 characterize an atypical Th2 response in ulcerative colitis. *J Clin Invest* **113**(10): 1490-1497.
- Gaffen, S. L. (2008). An overview of IL-17 function and signaling. *Cytokine* **43**(3): 402-407.
- Gaffen, S. L. and Hajishengallis, G. (2008). A new inflammatory cytokine on the block: re-thinking periodontal disease and the Th1/Th2 paradigm in the context of Th17 cells and IL-17. *J Dent Res* **87**(9): 817-828.
- Garcia Rodriguez, L. A., Gonzalez-Perez, A., Johansson, S. and Wallander, M. A. (2005). Risk factors for inflammatory bowel disease in the general population. *Aliment Pharmacol Ther* **22**(4): 309-315.
- Garcia Rodriguez, L. A., Ruigomez, A. and Panes, J. (2006). Acute gastroenteritis is followed by an increased risk of inflammatory bowel disease. *Gastroenterology* **130**(6): 1588-1594.
- Garolla, A., D'Inca, R., Checchin, D., Biagioli, A., De Toni, L., Nicoletti, V., Scarpa, M., Bolzonello, E., Sturniolo, G. C. and Foresta, C. (2009). Reduced Endothelial Progenitor Cell Number and Function in Inflammatory Bowel Disease: A Possible Link to the Pathogenesis. *Am J Gastroenterol*. Epub ahead of print.
- Garrett, W. S., Lord, G. M., Punit, S., Lugo-Villarino, G., Mazmanian, S. K., Ito, S., Glickman, J. N. and Glimcher, L. H. (2007). Communicable ulcerative colitis induced by T-bet deficiency in the innate immune system. *Cell* **131**(1): 33-45.

- Garrote, J. A., Arranz, E., Gomez-Gonzalez, E., Leon, A. J., Farre, C., Calvo, C., Bernardo, D., Fernandez-Salazar, L. and Blanco-Quiros, A. (2005). IL6, IL10 and TGFB1 gene polymorphisms in coeliac disease: differences between DQ2 positive and negative patients. Allergol Immunopathol (Madr) **33**(5): 245-249.
- Garrote, J. A., Gomez-Gonzalez, E., Bernardo, D., Arranz, E. and Chirdo, F. (2008). Celiac disease pathogenesis: the proinflammatory cytokine network. J Pediatr Gastroenterol Nutr **47 Suppl 1**: S27-32.
- Garside, P., Millington, O. and Smith, K. M. (2004). The anatomy of mucosal immune responses. Ann N Y Acad Sci **1029**: 9-15.
- Garside, P. and Mowat, A. M. (2001). Oral tolerance. Semin Immunol **13**(3): 177-185.
- Gersemann, M., Wehkamp, J., Fellermann, K. and Stange, E. F. (2008). Crohn's disease--defect in innate defence. World J Gastroenterol **14**(36): 5499-5503.
- Gershon, R. K. and Kondo, K. (1970). Cell interactions in the induction of tolerance: the role of thymic lymphocytes. Immunology **18**(5): 723-737.
- Gorard, D. A., Hunt, J. B., Payne-James, J. J., Palmer, K. R., Rees, R. G., Clark, M. L., Farthing, M. J., Misiewicz, J. J. and Silk, D. B. (1993). Initial response and subsequent course of Crohn's disease treated with elemental diet or prednisolone. Gut **34**(9): 1198-1202.
- Graff, L. A., Walker, J. R. and Bernstein, C. N. (2009). Depression and anxiety in inflammatory bowel disease: A review of comorbidity and management. Inflamm Bowel Dis **15**(7): 1105-1118.

Granzotto, M., Dal Bo, S., Quaglia, S., Tommasini, A., Piscianz, E., Valencic, E., Ferrara, F., Martelossi, S., Ventura, A. and Not, T. (2008). Regulatory T-Cell Function Is Impaired in Celiac Disease. Dig Dis Sci. **54**(7): 1513-1519.

Grossman, W. J., Verbsky, J. W., Tollefson, B. L., Kemper, C., Atkinson, J. P. and Ley, T. J. (2004). Differential expression of granzymes A and B in human cytotoxic lymphocyte subsets and T regulatory cells. Blood **104**(9): 2840-2848.

Guarner, F. and Malagelada, J. R. (2003). Gut flora in health and disease. Lancet **361**(9356): 512-519.

Guo, S., Cobb, D. and Smeltz, R. B. (2009). T-bet inhibits the in vivo differentiation of parasite-specific CD4+ Th17 cells in a T cell-intrinsic manner. J Immunol **182**(10): 6179-6186.

Hahm, K. B., Im, Y. H., Parks, T. W., Park, S. H., Markowitz, S., Jung, H. Y., Green, J. and Kim, S. J. (2001). Loss of transforming growth factor beta signalling in the intestine contributes to tissue injury in inflammatory bowel disease. Gut **49**(2): 190-198.

Hall, J. A., Bouladoux, N., Sun, C. M., Wohlfert, E. A., Blank, R. B., Zhu, Q., Grigg, M. E., Berzofsky, J. A. and Belkaid, Y. (2008). Commensal DNA limits regulatory T cell conversion and is a natural adjuvant of intestinal immune responses. Immunity **29**(4): 637-649.

Hanauer, S. B., Feagan, B. G., Lichtenstein, G. R., Mayer, L. F., Schreiber, S., Colombel, J. F., Rachmilewitz, D., Wolf, D. C., Olson, A., Bao, W. and Rutgeerts, P. (2002). Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet **359**(9317): 1541-1549.

- Happel, K. I., Dubin, P. J., Zheng, M., Ghilardi, N., Lockhart, C., Quinton, L. J., Odden, A. R., Shellito, J. E., Bagby, G. J., Nelson, S. and Kolls, J. K. (2005). Divergent roles of IL-23 and IL-12 in host defense against *Klebsiella pneumoniae*. *J Exp Med* **202**(6): 761-769.
- Harrington, L. E., Hatton, R. D., Mangan, P. R., Turner, H., Murphy, T. L., Murphy, K. M. and Weaver, C. T. (2005). Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. *Nat Immunol* **6**(11): 1123-1132.
- Harris, K. M., Fasano, A. and Mann, D. L. (2008). Cutting edge: IL-1 controls the IL-23 response induced by gliadin, the etiologic agent in celiac disease. *J Immunol* **181**(7): 4457-4460.
- Harris, T. J., Grosso, J. F., Yen, H. R., Xin, H., Kortylewski, M., Albesiano, E., Hipkiss, E. L., Getnet, D., Goldberg, M. V., Maris, C. H., Housseau, F., Yu, H., Pardoll, D. M. and Drake, C. G. (2007). Cutting edge: An in vivo requirement for STAT3 signaling in TH17 development and TH17-dependent autoimmunity. *J Immunol* **179**(7): 4313-4317.
- Hart, A. L., Al-Hassi, H. O., Rigby, R. J., Bell, S. J., Emmanuel, A. V., Knight, S. C., Kamm, M. A. and Stagg, A. J. (2005). Characteristics of intestinal dendritic cells in inflammatory bowel diseases. *Gastroenterology* **129**(1): 50-65.
- Henckaerts, L., Figueroa, C., Vermeire, S. and Sans, M. (2008). The role of genetics in inflammatory bowel disease. *Curr Drug Targets* **9**(5): 361-368.
- Hirota, K., Yoshitomi, H., Hashimoto, M., Maeda, S., Teradaira, S., Sugimoto, N., Yamaguchi, T., Nomura, T., Ito, H., Nakamura, T., Sakaguchi, N. and Sakaguchi, S.

(2007). Preferential recruitment of CCR6-expressing Th17 cells to inflamed joints via CCL20 in rheumatoid arthritis and its animal model. J Exp Med **204**(12): 2803-2812.

Hoffmann, P., Eder, R., Boeld, T. J., Doser, K., Piseshka, B., Andreesen, R. and Edinger, M. (2006). Only the CD45RA+ subpopulation of CD4+CD25high T cells gives rise to homogeneous regulatory T-cell lines upon in vitro expansion. Blood **108**(13): 4260-4267.

Holmes, G. K., Prior, P., Lane, M. R., Pope, D. and Allan, R. N. (1989). Malignancy in coeliac disease--effect of a gluten free diet. Gut **30**(3): 333-338.

Holtkamp, W., Stollberg, T. and Reis, H. E. (1995). Serum interleukin-6 is related to disease activity but not disease specificity in inflammatory bowel disease. J Clin Gastroenterol **20**(2): 123-126.

Holtta, V., Klemetti, P., Sipponen, T., Westerholm-Ormio, M., Kociubinski, G., Salo, H., Rasanen, L., Kolho, K. L., Farkkila, M., Savilahti, E. and Vaarala, O. (2008). IL-23/IL-17 immunity as a hallmark of Crohn's disease. Inflamm Bowel Dis **14**(9): 1175-1184.

Hori, S., Nomura, T. and Sakaguchi, S. (2003). Control of regulatory T cell development by the transcription factor Foxp3. Science **299**(5609): 1057-1061.

Hori, S. and Sakaguchi, S. (2004). Foxp3: a critical regulator of the development and function of regulatory T cells. Microbes Infect **6**(8): 745-751.

Horwitz, D. A., Zheng, S. G. and Gray, J. D. (2008). Natural and TGF-beta-induced Foxp3(+)CD4(+) CD25(+) regulatory T cells are not mirror images of each other. Trends Immunol **29**(9): 429-435.

- Hourigan, C. S. (2006). The molecular basis of coeliac disease. Clin Exp Med **6**(2): 53-59.
- Huan, J., Culbertson, N., Spencer, L., Bartholomew, R., Burrows, G. G., Chou, Y. K., Bourdette, D., Ziegler, S. F., Offner, H. and Vandenbark, A. A. (2005). Decreased FOXP3 levels in multiple sclerosis patients. J Neurosci Res **81**(1): 45-52.
- Hue, S., Ahern, P., Buonocore, S., Kullberg, M. C., Cua, D. J., McKenzie, B. S., Powrie, F. and Maloy, K. J. (2006). Interleukin-23 drives innate and T cell-mediated intestinal inflammation. J Exp Med **203**(11): 2473-2483.
- Hugot, J. P., Alberti, C., Berrebi, D., Bingen, E. and Cezard, J. P. (2003). Crohn's disease: the cold chain hypothesis. Lancet **362**(9400): 2012-2015.
- Hugot, J. P., Chamaillard, M., Zouali, H., Lesage, S., Cezard, J. P., Belaiche, J., Almer, S., Tysk, C., O'Morain, C. A., Gassull, M., Binder, V., Finkel, Y., Cortot, A., Modigliani, R., Laurent-Puig, P., Gower-Rousseau, C., Macry, J., Colombel, J. F., Sahbatou, M. and Thomas, G. (2001). Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. Nature **411**(6837): 599-603.
- Hunt, K. A., Zhernakova, A., Turner, G., Heap, G. A., Franke, L., Bruinenberg, M., Romanos, J., Dinesen, L. C., Ryan, A. W., Panesar, D., Gwilliam, R., Takeuchi, F., McLaren, W. M., Holmes, G. K., Howdle, P. D., Walters, J. R., Sanders, D. S., Playford, R. J., Trynka, G., Mulder, C. J., Mearin, M. L., Verbeek, W. H., Trimble, V., Stevens, F. M., O'Morain, C., Kennedy, N. P., Kelleher, D., Pennington, D. J., Strachan, D. P., McArdle, W. L., Mein, C. A., Wapenaar, M. C., Deloukas, P., McGinnis, R., McManus, R., Wijmenga, C. and van Heel, D. A. (2008). Newly identified genetic risk variants for celiac disease related to the immune response. Nat Genet **40**(4): 395-402.

- Hwang, J. M. and Varma, M. G. (2008). Surgery for inflammatory bowel disease. World J Gastroenterol **14**(17): 2678-2690.
- Hwang, S. Y. and Kim, H. Y. (2005). Expression of IL-17 homologs and their receptors in the synovial cells of rheumatoid arthritis patients. Mol Cells **19**(2): 180-184.
- Hyams, J. S., Fitzgerald, J. E., Treem, W. R., Wyzga, N. and Kreutzer, D. L. (1993). Relationship of functional and antigenic interleukin 6 to disease activity in inflammatory bowel disease. Gastroenterology **104**(5): 1285-1292.
- Ichiyama, K., Yoshida, H., Wakabayashi, Y., Chinen, T., Saeki, K., Nakaya, M., Takaesu, G., Hori, S., Yoshimura, A. and Kobayashi, T. (2008). Foxp3 inhibits ROR γ T-mediated IL-17A mRNA transcription through direct interaction with ROR γ T. J Biol Chem **283**(25): 17003-17008.
- Infante-Duarte, C., Horton, H. F., Byrne, M. C. and Kamradt, T. (2000). Microbial lipopeptides induce the production of IL-17 in Th cells. J Immunol **165**(11): 6107-6115.
- Isaacs, K. L., Sartor, R. B. and Haskill, S. (1992). Cytokine messenger RNA profiles in inflammatory bowel disease mucosa detected by polymerase chain reaction amplification. Gastroenterology **103**(5): 1587-1595.
- Ito, H., Takazoe, M., Fukuda, Y., Hibi, T., Kusugami, K., Andoh, A., Matsumoto, T., Yamamura, T., Azuma, J., Nishimoto, N., Yoshizaki, K., Shimoyama, T. and Kishimoto, T. (2004). A pilot randomized trial of a human anti-interleukin-6 receptor monoclonal antibody in active Crohn's disease. Gastroenterology **126**(4): 989-996; discussion 947.

- Ivanov, II, Frutos Rde, L., Manel, N., Yoshinaga, K., Rifkin, D. B., Sartor, R. B., Finlay, B. B. and Littman, D. R. (2008). Specific microbiota direct the differentiation of IL-17-producing T-helper cells in the mucosa of the small intestine. Cell Host Microbe **4**(4): 337-349.
- Ivanov, II, McKenzie, B. S., Zhou, L., Tadokoro, C. E., Lepelley, A., Lafaille, J. J., Cua, D. J. and Littman, D. R. (2006). The orphan nuclear receptor ROR γ T directs the differentiation program of proinflammatory IL-17 $+$ T helper cells. Cell **126**(6): 1121-1133.
- Ivarsson, A., Hernell, O., Stenlund, H. and Persson, L. A. (2002). Breast-feeding protects against celiac disease. Am J Clin Nutr **75**(5): 914-921.
- Iwata, M., Eshima, Y. and Kagechika, H. (2003). Retinoic acids exert direct effects on T cells to suppress Th1 development and enhance Th2 development via retinoic acid receptors. Int Immunol **15**(8): 1017-1025.
- Iwata, M., Hirakiyama, A., Eshima, Y., Kagechika, H., Kato, C. and Song, S. Y. (2004). Retinoic acid imprints gut-homing specificity on T cells. Immunity **21**(4): 527-538.
- Janeway, C. A., Travers, P., Walport, M. and Shlomchik, M. (2001). The Immune System in Health and Disease. USA, Garland Publishing.
- Joetham, A., Takeda, K., Taube, C., Miyahara, N., Matsubara, S., Koya, T., Rha, Y. H., Dakhama, A. and Gelfand, E. W. (2007). Naturally occurring lung CD4(+)CD25(+) T cell regulation of airway allergic responses depends on IL-10 induction of TGF-beta. J Immunol **178**(3): 1433-1442.

- Johansson, C. and Kelsall, B. L. (2005). Phenotype and function of intestinal dendritic cells. *Semin Immunol* **17**(4): 284-294.
- Johrens, K., Anagnostopoulos, I. and Stein, H. (2005). T-bet expression patterns in coeliac disease, cryptic and overt enteropathy-type T-cell lymphoma. *Histopathology* **47**(4): 368-374.
- Jonuleit, H. and Schmitt, E. (2003). The regulatory T cell family: distinct subsets and their interrelations. *J Immunol* **171**(12): 6323-6327.
- Junqueira, L. C. and Carneiro, J. (2003). *Basic Histology: Text and Atlas. Tenth Edition*. USA, McGraw-Hill.
- Kajiura, T., Takeda, T., Sakata, S., Sakamoto, M., Hashimoto, M., Suzuki, H., Suzuki, M. and Benno, Y. (2008). Change of Intestinal Microbiota with Elemental Diet and Its Impact on Therapeutic Effects in a Murine Model of Chronic Colitis. *Dig Dis Sci*.
- Kalliliolas, G. D. and Liossis, S. N. (2008). The future of the IL-1 receptor antagonist anakinra: from rheumatoid arthritis to adult-onset Still's disease and systemic-onset juvenile idiopathic arthritis. *Expert Opin Investig Drugs* **17**(3): 349-359.
- Kaminuma, O., Kitamura, F., Miyatake, S., Yamaoka, K., Miyoshi, H., Inokuma, S., Tatsumi, H., Nemoto, S., Kitamura, N., Mori, A. and Hiroi, T. (2009). T-box 21 transcription factor is responsible for distorted T(H)2 differentiation in human peripheral CD4+ T cells. *J Allergy Clin Immunol* **123**(4): 813-823 e813.
- Kang, S. G., Lim, H. W., Andrisani, O. M., Broxmeyer, H. E. and Kim, C. H. (2007). Vitamin A metabolites induce gut-homing FoxP3+ regulatory T cells. *J Immunol* **179**(6): 3724-3733.

Kelsall, B. L. and Leon, F. (2005). Involvement of intestinal dendritic cells in oral tolerance, immunity to pathogens, and inflammatory bowel disease. Immunol Rev **206**: 132-148.

Kelsen, J., Agnholt, J., Hoffmann, H. J., Romer, J. L., Hvas, C. L. and Dahlerup, J. F. (2005). FoxP3(+)CD4(+)CD25(+) T cells with regulatory properties can be cultured from colonic mucosa of patients with Crohn's disease. Clin Exp Immunol **141**(3): 549-557.

Kikuchi, H., Itoh, J. and Fukuda, S. (2008). Chronic nicotine stimulation modulates the immune response of mucosal T cells to Th1-dominant pattern via nAChR by upregulation of Th1-specific transcriptional factor. Neurosci Lett **432**(3): 217-221.

Kim, C. H. (2008). Regulation of FoxP3 regulatory T cells and Th17 cells by retinoids. Clin Dev Immunol **2008**: 416910.

Kivling, A., Nilsson, L., Falth-Magnusson, K., Sollvander, S., Johanson, C. and Faresjo, M. (2008). Diverse foxp3 expression in children with type 1 diabetes and celiac disease. Ann N Y Acad Sci **1150**: 273-277.

Klemann, C., Raveney, B. J., Klemann, A. K., Ozawa, T., von Horsten, S., Shudo, K., Oki, S. and Yamamura, T. (2009). Synthetic Retinoid AM80 Inhibits Th17 Cells and Ameliorates Experimental Autoimmune Encephalomyelitis. Am J Pathol **174**(6): 2234-2245.

Klement, E., Cohen, R. V., Boxman, J., Joseph, A. and Reif, S. (2004). Breastfeeding and risk of inflammatory bowel disease: a systematic review with meta-analysis. Am J Clin Nutr **80**(5): 1342-1352.

Kobayashi, K. S., Chamaillard, M., Ogura, Y., Henegariu, O., Inohara, N., Nunez, G. and Flavell, R. A. (2005). Nod2-dependent regulation of innate and adaptive immunity in the intestinal tract. Science **307**(5710): 731-734.

Kobayashi, T., Okamoto, S., Hisamatsu, T., Kamada, N., Chinen, H., Saito, R., Kitazume, M. T., Nakazawa, A., Sugita, A., Koganei, K., Isobe, K. and Hibi, T. (2008). IL23 differentially regulates the Th1/Th17 balance in ulcerative colitis and Crohn's disease. Gut **57**(12): 1682-1689.

Kobayashi, T., Okamoto, S., Hisamatsu, T., Kamada, N., Chinen, H., Saito, R., Kitazume, M. T., Nakazawa, A., Sugita, A., Koganei, K., Isobe, K. I. and Hibi, T. (2008). IL-23 differentially regulates the Th1/Th17 balance in ulcerative colitis and Crohn's disease. Gut **57**(12): 1682-1689.

Koenen, H. J., Smeets, R. L., Vink, P. M., van Rijssen, E., Boots, A. M. and Joosten, I. (2008). Human CD25highFoxp3pos regulatory T cells differentiate into IL-17-producing cells. Blood **112**(6): 2340-2352.

Kolls, J. K. and Linden, A. (2004). Interleukin-17 family members and inflammation. Immunity **21**(4): 467-476.

Koloski, N. A., Bret, L. and Radford-Smith, G. (2008). Hygiene hypothesis in inflammatory bowel disease: a critical review of the literature. World J Gastroenterol **14**(2): 165-173.

Kopf, H., de la Rosa, G. M., Howard, O. M. and Chen, X. (2007). Rapamycin inhibits differentiation of Th17 cells and promotes generation of FoxP3+ T regulatory cells. Int Immunopharmacol **7**(13): 1819-1824.

- Korn, T., Bettelli, E., Gao, W., Awasthi, A., Jager, A., Strom, T. B., Oukka, M. and Kuchroo, V. K. (2007). IL-21 initiates an alternative pathway to induce proinflammatory T(H)17 cells. Nature **448**(7152): 484-487.
- Korn, T., Bettelli, E., Oukka, M. and Kuchroo, V. K. (2009). IL-17 and Th17 Cells. Annu Rev Immunol **27**: 485-517.
- Korn, T., Oukka, M., Kuchroo, V. and Bettelli, E. (2007). Th17 cells: effector T cells with inflammatory properties. Semin Immunol **19**(6): 362-371.
- Kotake, S., Sato, K., Kim, K. J., Takahashi, N., Udagawa, N., Nakamura, I., Yamaguchi, A., Kishimoto, T., Suda, T. and Kashiwazaki, S. (1996). Interleukin-6 and soluble interleukin-6 receptors in the synovial fluids from rheumatoid arthritis patients are responsible for osteoclast-like cell formation. J Bone Miner Res **11**(1): 88-95.
- Kountouras, J., Zavos, C. and Chatzopoulos, D. (2004). Immunomodulatory benefits of cyclosporine A in inflammatory bowel disease. J Cell Mol Med **8**(3): 317-328.
- Kryczek, I., Bruce, A. T., Gudjonsson, J. E., Johnston, A., Aphale, A., Vatan, L., Szeliga, W., Wang, Y., Liu, Y., Welling, T. H., Elder, J. T. and Zou, W. (2008). Induction of IL-17+ T cell trafficking and development by IFN-gamma: mechanism and pathological relevance in psoriasis. J Immunol **181**(7): 4733-4741.
- Kryczek, I., Wei, S., Zou, L., Altuwaijri, S., Szeliga, W., Kolls, J., Chang, A. and Zou, W. (2007). Cutting edge: Th17 and regulatory T cell dynamics and the regulation by IL-2 in the tumor microenvironment. J Immunol **178**(11): 6730-6733.

- Kucharzik, T., Maaser, C., Lugering, A., Kagnoff, M., Mayer, L., Targan, S. and Domschke, W. (2006). Recent understanding of IBD pathogenesis: implications for future therapies. *Inflamm Bowel Dis* **12**(11): 1068-1083.
- Kumar, V., Abbas, A. and Fausto, N. (2005). *Robbins and Cotran: Pathologic Basis of Disease. Seventh Edition*. Philadelphia, Pennsylvania, Elsevier Saunders.
- Kuniyasu, Y., Takahashi, T., Itoh, M., Shimizu, J., Toda, G. and Sakaguchi, S. (2000). Naturally anergic and suppressive CD25(+)CD4(+) T cells as a functionally and phenotypically distinct immunoregulatory T cell subpopulation. *Int Immunol* **12**(8): 1145-1155.
- La Cava, A. (2008). T-regulatory cells in systemic lupus erythematosus. *Lupus* **17**(5): 421-425.
- Lala, S., Ogura, Y., Osborne, C., Hor, S. Y., Bromfield, A., Davies, S., Ogunbiyi, O., Nunez, G. and Keshav, S. (2003). Crohn's disease and the NOD2 gene: a role for paneth cells. *Gastroenterology* **125**(1): 47-57.
- Lamoreaux, L., Roederer, M. and Koup, R. (2006). Intracellular cytokine optimization and standard operating procedure. *Nat Protoc* **1**(3): 1507-1516.
- Langrish, C. L., Chen, Y., Blumenschein, W. M., Mattson, J., Basham, B., Sedgwick, J. D., McClanahan, T., Kastelein, R. A. and Cua, D. J. (2005). IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. *J Exp Med* **201**(2): 233-240.
- Larsen, C. S. (1990). Activation of human T lymphocytes by phorbol-12,13-dibutyrate and ionomycin. *Scand J Immunol* **31**(3): 353-360.

- Laurence, A., Tato, C. M., Davidson, T. S., Kanno, Y., Chen, Z., Yao, Z., Blank, R. B., Meylan, F., Siegel, R., Hennighausen, L., Shevach, E. M. and O'Shea J, J. (2007). Interleukin-2 signaling via STAT5 constrains T helper 17 cell generation. Immunity **26**(3): 371-381.
- Lawson, C. A., Brown, A. K., Bejarano, V., Douglas, S. H., Burgoyne, C. H., Greenstein, A. S., Boylston, A. W., Emery, P., Ponchel, F. and Isaacs, J. D. (2006). Early rheumatoid arthritis is associated with a deficit in the CD4+CD25high regulatory T cell population in peripheral blood. Rheumatology (Oxford) **45**(10): 1210-1217.
- Leppkes, M., Becker, C., Ivanov, II, Hirth, S., Wirtz, S., Neufert, C., Pouly, S., Murphy, A. J., Valenzuela, D. M., Yancopoulos, G. D., Becher, B., Littman, D. R. and Neurath, M. F. (2009). RORgamma-expressing Th17 cells induce murine chronic intestinal inflammation via redundant effects of IL-17A and IL-17F. Gastroenterology **136**(1): 257-267.
- Levings, M. K., Sangregorio, R. and Roncarolo, M. G. (2001). 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.
- Levison, D., Reid, R., Burt, A., Harrison, D. and Flemming, S. (2008). Muir's Textbook of Pathology. Fourteenth Edition. London, Edward Arnold.
- Liu, M. F., Wang, C. R., Fung, L. L., Lin, L. H. and Tsai, C. N. (2005). The presence of cytokine-suppressive CD4+CD25+ T cells in the peripheral blood and synovial fluid of patients with rheumatoid arthritis. Scand J Immunol **62**(3): 312-317.
- Liu, W., Putnam, A. L., Xu-Yu, Z., Szot, G. L., Lee, M. R., Zhu, S., Gottlieb, P. A., Kapranov, P., Gingeras, T. R., Fazekas de St Groth, B., Clayberger, C., Soper, D. M.,

Ziegler, S. F. and Bluestone, J. A. (2006). CD127 expression inversely correlates with FoxP3 and suppressive function of human CD4+ T reg cells. J Exp Med **203**(7): 1701-1711.

Liu, Z., Yang, L., Cui, Y., Wang, X., Guo, C., Huang, Z., Kan, Q., Liu, Z. and Liu, Y. (2009). Il-21 enhances NK cell activation and cytolytic activity and induces Th17 cell differentiation in inflammatory bowel disease. Inflamm Bowel Dis **15**(8): 1133-1144.

Liu, Z., Yang, L., Cui, Y., Wang, X., Guo, C., Huang, Z., Kan, Q., Liu, Z. and Liu, Y. (2009). Il-21 enhances NK cell activation and cytolytic activity and induces Th17 cell differentiation in inflammatory bowel disease. Inflamm Bowel Dis.

Lochner, M., Peduto, L., Cherrier, M., Sawa, S., Langa, F., Varona, R., Riethmacher, D., Si-Tahar, M., Di Santo, J. P. and Eberl, G. (2008). In vivo equilibrium of proinflammatory IL-17+ and regulatory IL-10+ Foxp3+ ROR $\{\gamma\}t+$ T cells. J Exp Med **205**(6): 1381-1393.

Lock, C., Hermans, G., Pedotti, R., Brendolan, A., Schadt, E., Garren, H., Langer-Gould, A., Strober, S., Cannella, B., Allard, J., Klonowski, P., Austin, A., Lad, N., Kaminski, N., Galli, S. J., Oksenberg, J. R., Raine, C. S., Heller, R. and Steinman, L. (2002). Gene-microarray analysis of multiple sclerosis lesions yields new targets validated in autoimmune encephalomyelitis. Nat Med **8**(5): 500-508.

Lodes, M. J., Cong, Y., Elson, C. O., Mohamath, R., Landers, C. J., Targan, S. R., Fort, M. and Hershberg, R. M. (2004). Bacterial flagellin is a dominant antigen in Crohn disease. J Clin Invest **113**(9): 1296-1306.

Longobardi-Given, A. (1992). Flow Cytometry: First Principles New York, USA, Library of Congress.

- Louis, S., Braudeau, C., Giral, M., Dupont, A., Moizant, F., Robillard, N., Moreau, A., Soulillou, J. P. and Brouard, S. (2006). Contrasting CD25hiCD4+T cells/FOXP3 patterns in chronic rejection and operational drug-free tolerance. *Transplantation* **81**(3): 398-407.
- Lubberts, E., Joosten, L. A., van de Loo, F. A., van den Gersselaar, L. A. and van den Berg, W. B. (2000). Reduction of interleukin-17-induced inhibition of chondrocyte proteoglycan synthesis in intact murine articular cartilage by interleukin-4. *Arthritis Rheum* **43**(6): 1300-1306.
- Luci, C., Reynders, A., Ivanov, II, Cognet, C., Chiche, L., Chasson, L., Hardwigsen, J., Anguiano, E., Banchereau, J., Chaussabel, D., Dalod, M., Littman, D. R., Vivier, E. and Tomasello, E. (2009). Influence of the transcription factor RORgammat on the development of NKp46+ cell populations in gut and skin. *Nat Immunol* **10**(1): 75-82.
- MacDermott, R. P. and Stenson, W. F. (1988). Alterations of the immune system in ulcerative colitis and Crohn's disease. *Adv Immunol* **42**: 285-328.
- Macian, F., Im, S. H., Garcia-Cozar, F. J. and Rao, A. (2004). T-cell anergy. *Curr Opin Immunol* **16**(2): 209-216.
- Madretsma, S., Wolters, L. M., van Dijk, J. P., Tak, C. J., Feyenabend, C., Wilson, J. H. and Zijlstra, F. J. (1996). In-vivo effect of nicotine on cytokine production by human non-adherent mononuclear cells. *Eur J Gastroenterol Hepatol* **8**(10): 1017-1020.
- Maecker, H. T., Moon, J., Bhatia, S., Ghanekar, S. A., Maino, V. C., Payne, J. K., Kuus-Reichel, K., Chang, J. C., Summers, A., Clay, T. M., Morse, M. A., Lyerly, H. K., DeLaRosa, C., Ankerst, D. P. and Disis, M. L. (2005). Impact of cryopreservation on tetramer, cytokine flow cytometry, and ELISPOT. *BMC Immunol* **6**: 17.

- Maecker, H. T., Rinfret, A., D'Souza, P., Darden, J., Roig, E., Landry, C., Hayes, P., Birungi, J., Anzala, O., Garcia, M., Harari, A., Frank, I., Baydo, R., Baker, M., Holbrook, J., Ottinger, J., Lamoreaux, L., Epling, C. L., Sinclair, E., Suni, M. A., Punt, K., Calarota, S., El-Bahi, S., Alter, G., Maila, H., Kuta, E., Cox, J., Gray, C., Altfeld, M., Nougarede, N., Boyer, J., Tussey, L., Tobery, T., Bredt, B., Roederer, M., Koup, R., Maino, V. C., Weinhold, K., Pantaleo, G., Gilmour, J., Horton, H. and Sekaly, R. P. (2005). Standardization of cytokine flow cytometry assays. BMC Immunol **6**: 13.
- Maeda, S., Hsu, L. C., Liu, H., Bankston, L. A., Iimura, M., Kagnoff, M. F., Eckmann, L. and Karin, M. (2005). Nod2 mutation in Crohn's disease potentiates NF-kappaB activity and IL-1beta processing. Science **307**(5710): 734-738.
- Mahida, Y. R., Wu, K. and Jewell, D. P. (1989). Enhanced production of interleukin 1-beta by mononuclear cells isolated from mucosa with active ulcerative colitis of Crohn's disease. Gut **30**(6): 835-838.
- Main, A. N., Mills, P. R., Russell, R. I., Bronte-Stewart, J., Nelson, L. M., McLlland, A. and Shenkin, A. (1983). Vitamin A deficiency in Crohn's disease. Gut **24**(12): 1169-1175.
- Makita, S., Kanai, T., Oshima, S., Uraushihara, K., Totsuka, T., Sawada, T., Nakamura, T., Koganei, K., Fukushima, T. and Watanabe, M. (2004). CD4+CD25bright T cells in human intestinal lamina propria as regulatory cells. J Immunol **173**(5): 3119-3130.
- Manel, N., Unutmaz, D. and Littman, D. R. (2008). The differentiation of human T(H)-17 cells requires transforming growth factor-beta and induction of the nuclear receptor RORgammat. Nat Immunol **9**(6): 641-649.

- Mangan, P. R., Harrington, L. E., O'Quinn, D. B., Helms, W. S., Bullard, D. C., Elson, C. O., Hatton, R. D., Wahl, S. M., Schoeb, T. R. and Weaver, C. T. (2006). Transforming growth factor-beta induces development of the T(H)17 lineage. Nature **441**(7090): 231-234.
- Marek, A., Brodzicki, J., Liberek, A. and Korzon, M. (2002). TGF-beta (transforming growth factor-beta) in chronic inflammatory conditions - a new diagnostic and prognostic marker? Med Sci Monit **8**(7): RA145-151.
- Marie, J. C., Letterio, J. J., Gavin, M. and Rudensky, A. Y. (2005). TGF-beta1 maintains suppressor function and Foxp3 expression in CD4+CD25+ regulatory T cells. J Exp Med **201**(7): 1061-1067.
- Martin, S. (2008). Against the grain: An overview of celiac disease. J Am Acad Nurse Pract **20**(5): 243-250.
- Mathur, A. N., Chang, H. C., Zisoulis, D. G., Stritesky, G. L., Yu, Q., O'Malley, J. T., Kapur, R., Levy, D. E., Kansas, G. S. and Kaplan, M. H. (2007). Stat3 and Stat4 direct development of IL-17-secreting Th cells. J Immunol **178**(8): 4901-4907.
- Matusevicius, D., Kivisakk, P., He, B., Kostulas, N., Ozenci, V., Fredrikson, S. and Link, H. (1999). Interleukin-17 mRNA expression in blood and CSF mononuclear cells is augmented in multiple sclerosis. Mult Scler **5**(2): 101-104.
- Maul, J., Loddenkemper, C., Mundt, P., Berg, E., Giese, T., Stallmach, A., Zeitz, M. and Duchmann, R. (2005). Peripheral and intestinal regulatory CD4+ CD25(high) T cells in inflammatory bowel disease. Gastroenterology **128**(7): 1868-1878.

- Mayer, L. and Shao, L. (2004). Therapeutic potential of oral tolerance. Nat Rev Immunol **4**(6): 407-419.
- McAlindon, M. E., Hawkey, C. J. and Mahida, Y. R. (1998). Expression of interleukin 1 beta and interleukin 1 beta converting enzyme by intestinal macrophages in health and inflammatory bowel disease. Gut **42**(2): 214-219.
- McCullough, F. S., Northrop-Clewes, C. A. and Thurnham, D. I. (1999). The effect of vitamin A on epithelial integrity. Proc Nutr Soc **58**(2): 289-293.
- McKinley, L., Alcorn, J. F., Peterson, A., Dupont, R. B., Kapadia, S., Logar, A., Henry, A., Irvin, C. G., Piganelli, J. D., Ray, A. and Kolls, J. K. (2008). TH17 cells mediate steroid-resistant airway inflammation and airway hyperresponsiveness in mice. J Immunol **181**(6): 4089-4097.
- Meresse, B., Verdier, J. and Cerf-Bensussan, N. (2008). The cytokine interleukin 21: a new player in coeliac disease? Gut **57**(7): 879-881.
- Merkle, C. J. (2005). Handbook of Pathophysiology. Philadelphia, Lippincott, Williams and Wilkins.
- Mitsuyama, K., Sata, M. and Rose-John, S. (2006). Interleukin-6 trans-signaling in inflammatory bowel disease. Cytokine Growth Factor Rev **17**(6): 451-461.
- Mitsuyama, K., Toyonaga, A., Sasaki, E., Ishida, O., Ikeda, H., Tsuruta, O., Harada, K., Tateishi, H., Nishiyama, T. and Tanikawa, K. (1995). Soluble interleukin-6 receptors in inflammatory bowel disease: relation to circulating interleukin-6. Gut **36**(1): 45-49.
- Mizoguchi, A., Ogawa, A., Takedatsu, H., Sugimoto, K., Shimomura, Y., Shirane, K., Nagahama, K., Nagaishi, T., Mizoguchi, E., Blumberg, R. S. and Bhan, A. K. (2007).

Dependence of intestinal granuloma formation on unique myeloid DC-like cells. J Clin Invest **117**(3): 605-615.

Moehle, C., Ackermann, N., Langmann, T., Aslanidis, C., Kel, A., Kel-Margoulis, O., Schmitz-Madry, A., Zahn, A., Stremmel, W. and Schmitz, G. (2006). Aberrant intestinal expression and allelic variants of mucin genes associated with inflammatory bowel disease. J Mol Med **84**(12): 1055-1066.

Molet, S., Hamid, Q., Davoine, F., Nutku, E., Taha, R., Page, N., Olivenstein, R., Elias, J. and Chakir, J. (2001). IL-17 is increased in asthmatic airways and induces human bronchial fibroblasts to produce cytokines. J Allergy Clin Immunol **108**(3): 430-438.

Monteleone, G., Monteleone, I., Fina, D., Vavassori, P., Del Vecchio Blanco, G., Caruso, R., Tersigni, R., Alessandroni, L., Biancone, L., Naccari, G. C., MacDonald, T. T. and Pallone, F. (2005). Interleukin-21 enhances T-helper cell type I signaling and interferon-gamma production in Crohn's disease. Gastroenterology **128**(3): 687-694.

Monteleone, I., Monteleone, G., Del Vecchio Blanco, G., Vavassori, P., Cucchiara, S., MacDonald, T. T. and Pallone, F. (2004). Regulation of the T helper cell type 1 transcription factor T-bet in coeliac disease mucosa. Gut **53**(8): 1090-1095.

Moo-Young, T. A., Larson, J. W., Belt, B. A., Tan, M. C., Hawkins, W. G., Eberlein, T. J., Goedegebuure, P. S. and Linehan, D. C. (2009). Tumor-derived TGF-beta mediates conversion of CD4+Foxp3+ regulatory T cells in a murine model of pancreas cancer. J Immunother **32**(1): 12-21.

Moreau, N. M., Martin, L. J., Toquet, C. S., Laboisse, C. L., Nguyen, P. G., Siliart, B. S., Dumon, H. J. and Champ, M. M. (2003). Restoration of the integrity of rat caeco-

colonic mucosa by resistant starch, but not by fructo-oligosaccharides, in dextran sulfate sodium-induced experimental colitis. Br J Nutr **90**(1): 75-85.

Mosmann, T. R., Cherwinski, H., Bond, M. W., Giedlin, M. A. and Coffman, R. L. (1986). Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. J Immunol **136**(7): 2348-2357.

Mosmann, T. R. and Coffman, R. L. (1989). TH1 and TH2 cells: different patterns of lymphokine secretion lead to different functional properties. Annu Rev Immunol **7**: 145-173.

Moss, A. C., Fernandez-Becker, N., Jo Kim, K., Cury, D. and Cheifetz, A. S. (2008). The impact of infliximab infusion reactions on long-term outcomes in patients with Crohn's disease. Aliment Pharmacol Ther **28**(2): 221-227.

Mottet, C., Uhlig, H. H. and Powrie, F. (2003). Cutting edge: cure of colitis by CD4+CD25+ regulatory T cells. J Immunol **170**(8): 3939-3943.

Mottonen, M., Heikkinen, J., Mustonen, L., Isomaki, P., Luukkainen, R. and Lassila, O. (2005). CD4+ CD25+ T cells with the phenotypic and functional characteristics of regulatory T cells are enriched in the synovial fluid of patients with rheumatoid arthritis. Clin Exp Immunol **140**(2): 360-367.

Mowat, A. M. (2003). Coeliac disease--a meeting point for genetics, immunology, and protein chemistry. Lancet **361**(9365): 1290-1292.

Mucida, D., Park, Y., Kim, G., Turovskaya, O., Scott, I., Kronenberg, M. and Cheroutre, H. (2007). Reciprocal TH17 and regulatory T cell differentiation mediated by retinoic acid. Science **317**(5835): 256-260.

- Mudter, J. and Neurath, M. F. (2007). IL-6 signaling in inflammatory bowel disease: pathophysiological role and clinical relevance. *Inflamm Bowel Dis* **13**(8): 1016-1023.
- Murphy, C. A., Langrish, C. L., Chen, Y., Blumenschein, W., McClanahan, T., Kastelein, R. A., Sedgwick, J. D. and Cua, D. J. (2003). Divergent pro- and antiinflammatory roles for IL-23 and IL-12 in joint autoimmune inflammation. *J Exp Med* **198**(12): 1951-1957.
- Murphy, K. M. and Reiner, S. L. (2002). The lineage decisions of helper T cells. *Nat Rev Immunol* **2**(12): 933-944.
- Nakae, S., Nambu, A., Sudo, K. and Iwakura, Y. (2003). Suppression of immune induction of collagen-induced arthritis in IL-17-deficient mice. *J Immunol* **171**(11): 6173-6177.
- Nakayama, T. and Yamashita, M. (2008). Initiation and maintenance of Th2 cell identity. *Curr Opin Immunol* **20**(3): 265-271.
- Nelson, B. H. and Willerford, D. M. (1998). Biology of the interleukin-2 receptor. *Adv Immunol* **70**: 1-81.
- Ng, E. K., Panesar, N., Longo, W. E., Shapiro, M. J., Kaminski, D. L., Tolman, K. C. and Mazuski, J. E. (2003). Human intestinal epithelial and smooth muscle cells are potent producers of IL-6. *Mediators Inflamm* **12**(1): 3-8.
- Nielsen, J., Holm, T. L. and Claesson, M. H. (2004). CD4+CD25+ regulatory T cells: II. Origin, disease models and clinical aspects. *Apmis* **112**(10): 642-650.

Nielsen, O. H., Kirman, I., Rudiger, N., Hendel, J. and Vainer, B. (2003). Upregulation of interleukin-12 and -17 in active inflammatory bowel disease. Scand J Gastroenterol **38**(2): 180-185.

Niessner, M. and Volk, B. A. (1995). Altered Th1/Th2 cytokine profiles in the intestinal mucosa of patients with inflammatory bowel disease as assessed by quantitative reversed transcribed polymerase chain reaction (RT-PCR). Clin Exp Immunol **101**(3): 428-435.

Niewinski, M. M. (2008). Advances in celiac disease and gluten-free diet. J Am Diet Assoc **108**(4): 661-672.

Nilsen, E. M., JahnSEN, F. L., Lundin, K. E., Johansen, F. E., Fausa, O., Sollid, L. M., JahnSEN, J., Scott, H. and Brandtzaeg, P. (1998). Gluten induces an intestinal cytokine response strongly dominated by interferon gamma in patients with celiac disease. Gastroenterology **115**(3): 551-563.

Nilsen, E. M., Lundin, K. E., Krajci, P., Scott, H., Sollid, L. M. and Brandtzaeg, P. (1995). Gluten specific, HLA-DQ restricted T cells from coeliac mucosa produce cytokines with Th1 or Th0 profile dominated by interferon gamma. Gut **37**(6): 766-776.

Nishikawa, J., Kudo, T., Sakata, S., Benno, Y. and Sugiyama, T. (2009). Diversity of mucosa-associated microbiota in active and inactive ulcerative colitis. Scand J Gastroenterol **44**(2): 180-186.

Nistala, K., Moncrieffe, H., Newton, K. R., Varsani, H., Hunter, P. and Wedderburn, L. R. (2008). Interleukin-17-producing T cells are enriched in the joints of children with arthritis, but have a reciprocal relationship to regulatory T cell numbers. Arthritis Rheum **58**(3): 875-887.

- Nurieva, R., Yang, X. O., Martinez, G., Zhang, Y., Panopoulos, A. D., Ma, L., Schluns, K., Tian, Q., Watowich, S. S., Jetten, A. M. and Dong, C. (2007). Essential autocrine regulation by IL-21 in the generation of inflammatory T cells. *Nature* **448**(7152): 480-483.
- O'Garra, A. and Murphy, K. (1994). Role of cytokines in determining T-lymphocyte function. *Curr Opin Immunol* **6**(3): 458-466.
- O'Gorman, M. R. and Zijenah, L. S. (2008). CD4 T cell measurements in the management of antiretroviral therapy--A review with an emphasis on pediatric HIV-infected patients. *Cytometry B Clin Cytom* **74 Suppl 1**: S19-26.
- Ogura, Y., Bonen, D. K., Inohara, N., Nicolae, D. L., Chen, F. F., Ramos, R., Britton, H., Moran, T., Karaliuskas, R., Duerr, R. H., Achkar, J. P., Brant, S. R., Bayless, T. M., Kirschner, B. S., Hanauer, S. B., Nunez, G. and Cho, J. H. (2001). A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. *Nature* **411**(6837): 603-606.
- Oppmann, B., Lesley, R., Blom, B., Timans, J. C., Xu, Y., Hunte, B., Vega, F., Yu, N., Wang, J., Singh, K., Zonin, F., Vaisberg, E., Churakova, T., Liu, M., Gorman, D., Wagner, J., Zurawski, S., Liu, Y., Abrams, J. S., Moore, K. W., Rennick, D., de Waal-Malefyt, R., Hannum, C., Bazan, J. F. and Kastelein, R. A. (2000). 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**(5): 715-725.
- Ott, S. J., Musfeldt, M., Wenderoth, D. F., Hampe, J., Brant, O., Folsch, U. R., Timmis, K. N. and Schreiber, S. (2004). Reduction in diversity of the colonic mucosa associated

bacterial microflora in patients with active inflammatory bowel disease. Gut **53**(5): 685-693.

Ouyang, W., Filvaroff, E., Hu, Y. and Grogan, J. (2009). Novel therapeutic targets along the Th17 pathway. Eur J Immunol **39**(3): 670-675.

Ouyang, W., Kolls, J. K. and Zheng, Y. (2008). The biological functions of T helper 17 cell effector cytokines in inflammation. Immunity **28**(4): 454-467.

Packey, C. D. and Sartor, R. B. (2008). Interplay of commensal and pathogenic bacteria, genetic mutations, and immunoregulatory defects in the pathogenesis of inflammatory bowel diseases. J Intern Med **263**(6): 597-606.

Padberg, F., Feneberg, W., Schmidt, S., Schwarz, M. J., Korschenhausen, D., Greenberg, B. D., Nolde, T., Muller, N., Trapmann, H., Konig, N., Moller, H. J. and Hampel, H. (1999). CSF and serum levels of soluble interleukin-6 receptors (sIL-6R and sgp130), but not of interleukin-6 are altered in multiple sclerosis. J Neuroimmunol **99**(2): 218-223.

Palmer, M. J., Mahajan, V. S., Trajman, L. C., Irvine, D. J., Lauffenburger, D. A. and Chen, J. (2008). Interleukin-7 receptor signaling network: an integrated systems perspective. Cell Mol Immunol **5**(2): 79-89.

Pan, Q., Mathison, J., Fearn, C., Kravchenko, V. V., Da Silva Correia, J., Hoffman, H. M., Kobayashi, K. S., Bertin, J., Grant, E. P., Coyle, A. J., Sutterwala, F. S., Ogura, Y., Flavell, R. A. and Ulevitch, R. J. (2007). MDP-induced interleukin-1beta processing requires Nod2 and CIAS1/NALP3. J Leukoc Biol **82**(1): 177-183.

- Pandian, P., Zheng, L., Ishihara, S., Reed, J. and Lenardo, M. J. (2007). CD4+CD25+Foxp3+ regulatory T cells induce cytokine deprivation-mediated apoptosis of effector CD4+ T cells. *Nat Immunol* **8**(12): 1353-1362.
- Papiernik, M., de Moraes, M. L., Pontoux, C., Vasseur, F. and Penit, C. (1998). Regulatory CD4 T cells: expression of IL-2R alpha chain, resistance to clonal deletion and IL-2 dependency. *Int Immunol* **10**(4): 371-378.
- Pasare, C. and Medzhitov, R. (2003). Toll pathway-dependent blockade of CD4+CD25+ T cell-mediated suppression by dendritic cells. *Science* **299**(5609): 1033-1036.
- Paust, S. and Cantor, H. (2005). Regulatory T cells and autoimmune disease. *Immunol Rev* **204**: 195-207.
- Peng, Y., Laouar, Y., Li, M. O., Green, E. A. and Flavell, R. A. (2004). TGF-beta regulates in vivo expansion of Foxp3-expressing CD4+CD25+ regulatory T cells responsible for protection against diabetes. *Proc Natl Acad Sci U S A* **101**(13): 4572-4577.
- Peters, J. H., Preijers, F. W., Woestenenk, R., Hilbrands, L. B., Koenen, H. J. and Joosten, I. (2008). Clinical grade Treg: GMP isolation, improvement of purity by CD127 Depletion, Treg expansion, and Treg cryopreservation. *PLoS ONE* **3**(9): e3161.
- Piccirillo, C. A. and Shevach, E. M. (2004). Naturally-occurring CD4+CD25+ immunoregulatory T cells: central players in the arena of peripheral tolerance. *Semin Immunol* **16**(2): 81-88.

- Pierik, M., Joossens, S., Van Steen, K., Van Schuerbeek, N., Vlietinck, R., Rutgeerts, P. and Vermeire, S. (2006). Toll-like receptor-1, -2, and -6 polymorphisms influence disease extension in inflammatory bowel diseases. *Inflamm Bowel Dis* **12**(1): 1-8.
- Piersma, S. J., Welters, M. J. and van der Burg, S. H. (2008). Tumor-specific regulatory T cells in cancer patients. *Hum Immunol* **69**(4-5): 241-249.
- Pignata, C., Troncone, R., Monaco, G., Ciriaco, M., Farris, E., Carminati, G. and Auricchio, S. (1985). Impaired suppressor activity in children affected by coeliac disease. *Gut* **26**(3): 285-290.
- Pillai, V., Ortega, S. B., Wang, C. K. and Karandikar, N. J. (2007). Transient regulatory T-cells: a state attained by all activated human T-cells. *Clin Immunol* **123**(1): 18-29.
- Plevy, S. (2002). The immunology of inflammatory bowel disease. *Gastroenterol Clin North Am* **31**(1): 77-92.
- Porth, C. (2005). *Pathophysiology: Concepts of Altered Health States*. Seventh Edition. Philadelphia. Lippincott Williams and Wilkins.
- Quintana, F. J., Basso, A. S., Iglesias, A. H., Korn, T., Farez, M. F., Bettelli, E., Caccamo, M., Oukka, M. and Weiner, H. L. (2008). Control of T(reg) and T(H)17 cell differentiation by the aryl hydrocarbon receptor. *Nature* **453**(7191): 65-71.
- Quintana, F. J. and Weiner, H. L. (2009). Environmental control of Th17 differentiation. *Eur J Immunol* **39**(3): 655-657.
- Raelson, J. V., Little, R. D., Ruether, A., Fournier, H., Paquin, B., Van Eerdewegh, P., Bradley, W. E., Croteau, P., Nguyen-Huu, Q., Segal, J., Debrus, S., Allard, R., Rosenstiel, P., Franke, A., Jacobs, G., Nikolaus, S., Vidal, J. M., Szego, P., Laplante,

N., Clark, H. F., Paulussen, R. J., Hooper, J. W., Keith, T. P., Belouchi, A. and Schreiber, S. (2007). Genome-wide association study for Crohn's disease in the Quebec Founder Population identifies multiple validated disease loci. Proc Natl Acad Sci U S A **104**(37): 14747-14752.

Read, S. and Powrie, F. (2001). CD4(+) regulatory T cells. Curr Opin Immunol **13**(6): 644-649.

Reimund, J. M., Wittersheim, C., Dumont, S., Muller, C. D., Kenney, J. S., Baumann, R., Poindron, P. and Duclos, B. (1996). Increased production of tumour necrosis factor-alpha interleukin-1 beta, and interleukin-6 by morphologically normal intestinal biopsies from patients with Crohn's disease. Gut **39**(5): 684-689.

Ricciardelli, I., Lindley, K. J., Londei, M. and Quaratino, S. (2008). Anti tumour necrosis-alpha therapy increases the number of FOXP3 regulatory T cells in children affected by Crohn's disease. Immunology **125**(2): 178-183.

Rioux, J. D., Xavier, R. J., Taylor, K. D., Silverberg, M. S., Goyette, P., Huett, A., Green, T., Kuballa, P., Barmada, M. M., Datta, L. W., Shugart, Y. Y., Griffiths, A. M., Targan, S. R., Ippoliti, A. F., Bernard, E. J., Mei, L., Nicolae, D. L., Regueiro, M., Schumm, L. P., Steinhart, A. H., Rotter, J. I., Duerr, R. H., Cho, J. H., Daly, M. J. and Brant, S. R. (2007). Genome-wide association study identifies new susceptibility loci for Crohn disease and implicates autophagy in disease pathogenesis. Nat Genet **39**(5): 596-604.

Rodriguez, P., Heyman, M., Candalh, C., Blaton, M. A. and Bouchaud, C. (1995). Tumour necrosis factor-alpha induces morphological and functional alterations of intestinal HT29 cl.19A cell monolayers. Cytokine **7**(5): 441-448.

- Romagnani, S. (2006). Regulation of the T cell response. Clin Exp Allergy **36**(11): 1357-1366.
- Romaldini, C. C., Barbieri, D., Okay, T. S., Raiz, R., Jr. and Cancado, E. L. (2002). Serum soluble interleukin-2 receptor, interleukin-6, and tumor necrosis factor-alpha levels in children with celiac disease: response to treatment. J Pediatr Gastroenterol Nutr **35**(4): 513-517.
- Roncarolo, M. G. and Gregori, S. (2008). Is FOXP3 a bona fide marker for human regulatory T cells? Eur J Immunol **38**(4): 925-927.
- Rong, G., Zhou, Y., Xiong, Y., Zhou, L., Geng, H., Jiang, T., Zhu, Y., Lu, H., Zhang, S., Wang, P., Zhang, B. and Zhong, R. (2009). Imbalance between T helper type 17 and T regulatory cells in patients with primary biliary cirrhosis: the serum cytokine profile and peripheral cell population. Clin Exp Immunol **156**(2): 217-225.
- Rostaing, L., Tkaczuk, J., Durand, M., Peres, C., Durand, D., de Preval, C., Ohayon, E. and Abbal, M. (1999). Kinetics of intracytoplasmic Th1 and Th2 cytokine production assessed by flow cytometry following in vitro activation of peripheral blood mononuclear cells. Cytometry B Clin Cytom **35**(4): 318-328.
- Rouvier, E., Luciani, M. F., Mattei, M. G., Denizot, F. and Golstein, P. (1993). CTLA-8, cloned from an activated T cell, bearing AU-rich messenger RNA instability sequences, and homologous to a herpesvirus saimiri gene. J Immunol **150**(12): 5445-5456.
- Rutella, S. and Lemoli, R. M. (2004). Regulatory T cells and tolerogenic dendritic cells: from basic biology to clinical applications. Immunol Lett **94**(1-2): 11-26.

- Rutgeerts, P., Vermeire, S. and Van Assche, G. (2009). Biological therapies for inflammatory bowel diseases. Gastroenterology **136**(4): 1182-1197.
- Ruyssers, N. E., De Winter, B. Y., De Man, J. G., Loukas, A., Herman, A. G., Pelckmans, P. A. and Moreels, T. G. (2008). Worms and the treatment of inflammatory bowel disease: are molecules the answer? Clin Dev Immunol **2008**: 567314.
- Sakaguchi, S., Sakaguchi, N., Asano, M., Itoh, M. and 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**(3): 1151-1164.
- Sakaguchi, S., Yamaguchi, T., Nomura, T. and Ono, M. (2008). Regulatory T cells and immune tolerance. Cell **133**(5): 775-787.
- Salvati, V. M., MacDonald, T. T., Bajaj-Elliott, M., Borrelli, M., Staiano, A., Auricchio, S., Troncone, R. and Monteleone, G. (2002). Interleukin 18 and associated markers of T helper cell type 1 activity in coeliac disease. Gut **50**(2): 186-190.
- Sanchez-Munoz, F., Dominguez-Lopez, A. and Yamamoto-Furusho, J. K. (2008). Role of cytokines in inflammatory bowel disease. World J Gastroenterol **14**(27): 4280-4288.
- Sandborn, W. J. (2008). Current directions in IBD therapy: what goals are feasible with biological modifiers? Gastroenterology **135**(5): 1442-1447.
- Sanderson, J. D., Moss, M. T., Tizard, M. L. and Hermon-Taylor, J. (1992). Mycobacterium paratuberculosis DNA in Crohn's disease tissue. Gut **33**(7): 890-896.

- Sanos, S. L., Bui, V. L., Mortha, A., Oberle, K., Heners, C., Johner, C. and Diefenbach, A. (2009). RORgammat and commensal microflora are required for the differentiation of mucosal interleukin 22-producing NKp46⁺ cells. *Nat Immunol* **10**(1): 83-91.
- Santarlasci, V., Maggi, L., Capone, M., Frosali, F., Querci, V., De Palma, R., Liotta, F., Cosmi, L., Maggi, E., Romagnani, S. and Annunziato, F. (2009). TGF-beta indirectly favors the development of human Th17 cells by inhibiting Th1 cells. *Eur J Immunol* **39**(1): 207-215.
- Sarkar, S. and Fox, D. A. (2008). Regulatory T cells in rheumatoid arthritis. *Curr Rheumatol Rep* **10**(5): 405-412.
- Sartor, R. B. (2004). Therapeutic manipulation of the enteric microflora in inflammatory bowel diseases: antibiotics, probiotics, and prebiotics. *Gastroenterology* **126**(6): 1620-1633.
- Schmidt, C., Giese, T., Ludwig, B., Mueller-Molaian, I., Marth, T., Zeuzem, S., Meuer, S. C. and Stallmach, A. (2005). Expression of interleukin-12-related cytokine transcripts in inflammatory bowel disease: elevated interleukin-23p19 and interleukin-27p28 in Crohn's disease but not in ulcerative colitis. *Inflamm Bowel Dis* **11**(1): 16-23.
- Schmidt-Weber, C. B. and Blaser, K. (2006). The role of TGF-beta in allergic inflammation. *Immunol Allergy Clin North Am* **26**(2): 233-244, vi-vii.
- Schuerwagh, A. J., Stevens, W. J., Bridts, C. H. and De Clerck, L. S. (2001). Evaluation of monensin and brefeldin A for flow cytometric determination of interleukin-1 beta, interleukin-6, and tumor necrosis factor-alpha in monocytes. *Cytometry B Clin Cytom* **46**(3): 172-176.

- Sears, C. L. (2005). A dynamic partnership: celebrating our gut flora. *Anaerobe* **11**(5): 247-251.
- Seddiki, N., Santner-Nanan, B., Martinson, J., Zaunders, J., Sasson, S., Landay, A., Solomon, M., Selby, W., Alexander, S. I., Nanan, R., Kelleher, A. and Fazekas de St Groth, B. (2006). Expression of interleukin (IL)-2 and IL-7 receptors discriminates between human regulatory and activated T cells. *J Exp Med* **203**(7): 1693-1700.
- Seddiki, N., Santner-Nanan, B., Tangye, S. G., Alexander, S. I., Solomon, M., Lee, S., Nanan, R. and Fazekas de Saint Groth, B. (2006). Persistence of naive CD45RA+ regulatory T cells in adult life. *Blood* **107**(7): 2830-2838.
- Sell, S. (2001). *Immunology, Immunopathology and Immunity*. Washington, DC, ASM Press.
- Setty, M., Hormaza, L. and Guandalini, S. (2008). Celiac disease: risk assessment, diagnosis, and monitoring. *Mol Diagn Ther* **12**(5): 289-298.
- Shen, L. S., Wang, J., Shen, D. F., Yuan, X. L., Dong, P., Li, M. X., Xue, J., Zhang, F. M., Ge, H. L. and Xu, D. (2009). CD4(+)CD25(+)CD127(low/-) regulatory T cells express Foxp3 and suppress effector T cell proliferation and contribute to gastric cancers progression. *Clin Immunol*.
- Shi, B., Wang, Z., Jin, H., Chen, Y. W., Wang, Q. and Qian, Y. (2009). Immunoregulatory Cordyceps sinensis increases regulatory T cells to Th17 cell ratio and delays diabetes in NOD mice. *Int Immunopharmacol* **9**(5): 582-586.

- Shi, G., Cox, C. A., Vistica, B. P., Tan, C., Wawrousek, E. F. and Gery, I. (2008). Phenotype switching by inflammation-inducing polarized Th17 cells, but not by Th1 cells. *J Immunol* **181**(10): 7205-7213.
- Shibolet, O., Regushevskaya, E., Brezis, M. and Soares-Weiser, K. (2005). Cyclosporine A for induction of remission in severe ulcerative colitis. *Cochrane Database Syst Rev*(1): CD004277.
- Siegmund, B. (2002). Interleukin-1beta converting enzyme (caspase-1) in intestinal inflammation. *Biochem Pharmacol* **64**(1): 1-8.
- Simon, P. (2003). Q-Gene: processing quantitative real-time RT-PCR data. *Bioinformatics* **19**(11): 1439-1440.
- Sitaraman, S. V., Klapproth, J. M., Moore, D. A., 3rd, Landers, C., Targan, S., Williams, I. R. and Gewirtz, A. T. (2005). Elevated flagellin-specific immunoglobulins in Crohn's disease. *Am J Physiol Gastrointest Liver Physiol* **288**(2): G403-406.
- Sitohy, B., Hammarstrom, S., Danielsson, A. and Hammarstrom, M. L. (2008). Basal lymphoid aggregates in ulcerative colitis colon: a site for regulatory T cell action. *Clin Exp Immunol* **151**(2): 326-333.
- Smits, H. H., van Beelen, A. J., Hessle, C., Westland, R., de Jong, E., Soeteman, E., Wold, A., Wierenga, E. A. and Kapsenberg, M. L. (2004). Commensal Gram-negative bacteria prime human dendritic cells for enhanced IL-23 and IL-27 expression and enhanced Th1 development. *Eur J Immunol* **34**(5): 1371-1380.
- Souza, H. S., Tortori, C. J., Castelo-Branco, M. T., Carvalho, A. T., Margallo, V. S., Delgado, C. F., Dines, I. and Elia, C. C. (2005). Apoptosis in the intestinal mucosa of

patients with inflammatory bowel disease: evidence of altered expression of FasL and perforin cytotoxic pathways. Int J Colorectal Dis **20**(3): 277-286.

Spada, C., Riccioni, M. E., Urgesi, R. and Costamagna, G. (2008). Capsule endoscopy in celiac disease. World J Gastroenterol **14**(26): 4146-4151.

Spolski, R. and Leonard, W. J. (2008). Interleukin-21: basic biology and implications for cancer and autoimmunity. Annu Rev Immunol **26**: 57-79.

Spolski, R. and Leonard, W. J. (2008). The Yin and Yang of interleukin-21 in allergy, autoimmunity and cancer. Curr Opin Immunol **20**(3): 295-301.

Stagg, A. J., Hart, A. L., Knight, S. C. and Kamm, M. A. (2003). The dendritic cell: its role in intestinal inflammation and relationship with gut bacteria. Gut **52**(10): 1522-1529.

Stamp, L. K., James, M. J. and Cleland, L. G. (2004). Interleukin-17: the missing link between T-cell accumulation and effector cell actions in rheumatoid arthritis? Immunol Cell Biol **82**(1): 1-9.

Steed, H., Macfarlane, G. T. and Macfarlane, S. (2008). Prebiotics, synbiotics and inflammatory bowel disease. Mol Nutr Food Res **52**(8): 898-905.

Stepniak, D. and Koning, F. (2006). Celiac disease--sandwiched between innate and adaptive immunity. Hum Immunol **67**(6): 460-468.

Stockinger, B., Veldhoen, M. and Hirota, K. (2009). Modulation of Th17 development and function by activation of the aryl hydrocarbon receptor--the role of endogenous ligands. Eur J Immunol **39**(3): 652-654.

- Stummvoll, G. H., DiPaolo, R. J., Huter, E. N., Davidson, T. S., Glass, D., Ward, J. M. and Shevach, E. M. (2008). Th1, Th2, and Th17 effector T cell-induced autoimmune gastritis differs in pathological pattern and in susceptibility to suppression by regulatory T cells. *J Immunol* **181**(3): 1908-1916.
- Summers, R. W., Elliott, D. E., Urban, J. F., Jr., Thompson, R. and Weinstock, J. V. (2005). *Trichuris suis* therapy in Crohn's disease. *Gut* **54**(1): 87-90.
- Swinson, C. M., Slavin, G., Coles, E. C. and Booth, C. C. (1983). Coeliac disease and malignancy. *Lancet* **1**(8316): 111-115.
- Takahashi, M., Nakamura, K., Honda, K., Kitamura, Y., Mizutani, T., Araki, Y., Kabemura, T., Chijiwa, Y., Harada, N. and Nawata, H. (2006). An inverse correlation of human peripheral blood regulatory T cell frequency with the disease activity of ulcerative colitis. *Dig Dis Sci* **51**(4): 677-686.
- Takaishi, H., Matsuki, T., Nakazawa, A., Takada, T., Kado, S., Asahara, T., Kamada, N., Sakuraba, A., Yajima, T., Higuchi, H., Inoue, N., Ogata, H., Iwao, Y., Nomoto, K., Tanaka, R. and Hibi, T. (2008). Imbalance in intestinal microflora constitution could be involved in the pathogenesis of inflammatory bowel disease. *Int J Med Microbiol* **298**(5-6): 463-472.
- Taurog, J. D., Richardson, J. A., Croft, J. T., Simmons, W. A., Zhou, M., Fernandez-Sueiro, J. L., Balish, E. and Hammer, R. E. (1994). The germfree state prevents development of gut and joint inflammatory disease in HLA-B27 transgenic rats. *J Exp Med* **180**(6): 2359-2364.

- Terpend, K., Boisgerault, F., Blaton, M. A., Desjeux, J. F. and Heyman, M. (1998). Protein transport and processing by human HT29-19A intestinal cells: effect of interferon gamma. Gut **42**(4): 538-545.
- Theofilopoulos, A. N., Koundouris, S., Kono, D. H. and Lawson, B. R. (2001). The role of IFN-gamma in systemic lupus erythematosus: a challenge to the Th1/Th2 paradigm in autoimmunity. Arthritis Res **3**(3): 136-141.
- Thompson, N. P., Pounder, R. E. and Wakefield, A. J. (1995). Perinatal and childhood risk factors for inflammatory bowel disease: a case-control study. Eur J Gastroenterol Hepatol **7**(5): 385-390.
- Thompson-Chagoyan, O. C., Maldonado, J. and Gil, A. (2005). Aetiology of inflammatory bowel disease (IBD): role of intestinal microbiota and gut-associated lymphoid tissue immune response. Clin Nutr **24**(3): 339-352.
- Thornton, A. M., Piccirillo, C. A. and Shevach, E. M. (2004). Activation requirements for the induction of CD4+CD25+ T cell suppressor function. Eur J Immunol **34**(2): 366-376.
- Thornton, A. M. and Shevach, E. M. (1998). CD4+CD25+ immunoregulatory T cells suppress polyclonal T cell activation in vitro by inhibiting interleukin 2 production. J Exp Med **188**(2): 287-296.
- Tiittanen, M., Westerholm-Ormio, M., Verkasalo, M., Savilahti, E. and Vaarala, O. (2008). Infiltration of forkhead box P3-expressing cells in small intestinal mucosa in coeliac disease but not in type 1 diabetes. Clin Exp Immunol **152**(3): 498-507.

Torchinsky, M. B., Garaude, J., Martin, A. P. and Blander, J. M. (2009). Innate immune recognition of infected apoptotic cells directs T(H)17 cell differentiation. Nature **458**(7234): 78-82.

Torok, H. P., Glas, J., Endres, I., Tonenchi, L., Teshome, M. Y., Wetzke, M., Klein, W., Lohse, P., Ochsenkuhn, T., Folwaczny, M., Goke, B., Folwaczny, C., Muller-Myhsok, B. and Brand, S. (2009). Epistasis Between Toll-Like Receptor-9 Polymorphisms and Variants in NOD2 and IL23R Modulates Susceptibility to Crohn's Disease. Am J Gastroenterol.

Torres, M. I. and Rios, A. (2008). Current view of the immunopathogenesis in inflammatory bowel disease and its implications for therapy. World J Gastroenterol **14**(13): 1972-1980.

Troncone, R., Gianfrani, C., Mazzarella, G., Greco, L., Guardiola, J., Auricchio, S. and De Berardinis, P. (1998). Majority of gliadin-specific T-cell clones from celiac small intestinal mucosa produce interferon-gamma and interleukin-4. Dig Dis Sci **43**(1): 156-161.

Uematsu, S., Fujimoto, K., Jang, M. H., Yang, B. G., Jung, Y. J., Nishiyama, M., Sato, S., Tsujimura, T., Yamamoto, M., Yokota, Y., Kiyono, H., Miyasaka, M., Ishii, K. J. and Akira, S. (2008). Regulation of humoral and cellular gut immunity by lamina propria dendritic cells expressing Toll-like receptor 5. Nat Immunol **9**(7): 769-776.

Ulfgren, A. K., Grondal, L., Lindblad, S., Khademi, M., Johnell, O., Klareskog, L. and Andersson, U. (2000). Interindividual and intra-articular variation of proinflammatory cytokines in patients with rheumatoid arthritis: potential implications for treatment. Ann Rheum Dis **59**(6): 439-447.

- Ulfgren, A. K., Lindblad, S., Klareskog, L., Andersson, J. and Andersson, U. (1995). Detection of cytokine producing cells in the synovial membrane from patients with rheumatoid arthritis. Ann Rheum Dis **54**(8): 654-661.
- Valmori, D., Merlo, A., Souleimanian, N. E., Hesdorffer, C. S. and Ayyoub, M. (2005). A peripheral circulating compartment of natural naive CD4 Tregs. J Clin Invest **115**(7): 1953-1962.
- van Amelsfort, J. M., Jacobs, K. M., Bijlsma, J. W., Lafeber, F. P. and Taams, L. S. (2004). CD4(+)CD25(+) regulatory T cells in rheumatoid arthritis: differences in the presence, phenotype, and function between peripheral blood and synovial fluid. Arthritis Rheum **50**(9): 2775-2785.
- Van der Sluis, M., De Koning, B. A., De Bruijn, A. C., Velcich, A., Meijerink, J. P., Van Goudoever, J. B., Buller, H. A., Dekker, J., Van Seuningen, I., Renes, I. B. and Einerhand, A. W. (2006). Muc2-deficient mice spontaneously develop colitis, indicating that MUC2 is critical for colonic protection. Gastroenterology **131**(1): 117-129.
- van Hamburg, J. P., de Bruijn, M. J., Ribeiro de Almeida, C., van Zwam, M., van Meurs, M., de Haas, E., Boon, L., Samsom, J. N. and Hendriks, R. W. (2008). Enforced expression of GATA3 allows differentiation of IL-17-producing cells, but constrains Th17-mediated pathology. Eur J Immunol **38**(9): 2573-2586.
- van Hamburg, J. P., Mus, A. M., de Bruijn, M. J., de Vogel, L., Boon, L., Cornelissen, F., Asmawidjaja, P., Hendriks, R. W. and Lubberts, E. (2009). GATA-3 protects against severe joint inflammation and bone erosion and reduces differentiation of Th17 cells during experimental arthritis. Arthritis Rheum **60**(3): 750-759.

van Heel, D. A. and West, J. (2006). Recent advances in coeliac disease. Gut **55**(7): 1037-1046.

Van Kemseke, C., Belaiche, J. and Louis, E. (2000). Frequently relapsing Crohn's disease is characterized by persistent elevation in interleukin-6 and soluble interleukin-2 receptor serum levels during remission. Int J Colorectal Dis **15**(4): 206-210.

van Riet, E., Hartgers, F. C. and Yazdanbakhsh, M. (2007). Chronic helminth infections induce immunomodulation: consequences and mechanisms. Immunobiology **212**(6): 475-490.

Van Snick, J. (1990). Interleukin-6: an overview. Annu Rev Immunol **8**: 253-278.

Vanderpool, C., Yan, F. and Polk, D. B. (2008). Mechanisms of probiotic action: Implications for therapeutic applications in inflammatory bowel diseases. Inflamm Bowel Dis **14**(11): 1585-1596.

Veldhoen, M., Hocking, R. J., Atkins, C. J., Locksley, R. M. and Stockinger, B. (2006). TGFbeta in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells. Immunity **24**(2): 179-189.

Veldhoen, M., Hocking, R. J., Flavell, R. A. and Stockinger, B. (2006). Signals mediated by transforming growth factor-beta initiate autoimmune encephalomyelitis, but chronic inflammation is needed to sustain disease. Nat Immunol **7**(11): 1151-1156.

Venken, K., Hellings, N., Hensen, K., Rummens, J. L., Medaer, R., D'Hooghe M, B., Dubois, B., Raus, J. and Stinissen, P. (2006). Secondary progressive in contrast to relapsing-remitting multiple sclerosis patients show a normal CD4+CD25+ regulatory T-cell function and FOXP3 expression. J Neurosci Res **83**(8): 1432-1446.

- Venken, K., Thewissen, M., Hellings, N., Somers, V., Hensen, K., Rummens, J. L. and Stinissen, P. (2007). A CFSE based assay for measuring CD4+CD25+ regulatory T cell mediated suppression of auto-antigen specific and polyclonal T cell responses. *J Immunol Methods* **322**(1-2): 1-11.
- Verbeek, W. H., von Blomberg, B. M., Coupe, V. M., Daum, S., Mulder, C. J. and Schreurs, M. W. (2009). Aberrant T-lymphocytes in refractory coeliac disease are not strictly confined to a small intestinal intraepithelial localization. *Cytometry B Clin Cytom.* Epub ahead of print
- Videla, S., Vilaseca, J., Antolin, M., Garcia-Lafuente, A., Guarner, F., Crespo, E., Casalots, J., Salas, A. and Malagelada, J. R. (2001). Dietary inulin improves distal colitis induced by dextran sodium sulfate in the rat. *Am J Gastroenterol* **96**(5): 1486-1493.
- Vieira, P. L., de Jong, E. C., Wierenga, E. A., Kapsenberg, M. L. and Kalinski, P. (2000). Development of Th1-inducing capacity in myeloid dendritic cells requires environmental instruction. *J Immunol* **164**(9): 4507-4512.
- Viglietta, V., Baecher-Allan, C., Weiner, H. L. and Hafler, D. A. (2004). Loss of functional suppression by CD4+CD25+ regulatory T cells in patients with multiple sclerosis. *J Exp Med* **199**(7): 971-979.
- Vignali, D. A., Collison, L. W. and Workman, C. J. (2008). How regulatory T cells work. *Nat Rev Immunol* **8**(7): 523-532.
- Vincenti, F. (2008). Costimulation blockade in autoimmunity and transplantation. *J Allergy Clin Immunol* **121**(2): 299-306.

- Volpe, E., Servant, N., Zollinger, R., Bogiatzi, S. I., Hupe, P., Barillot, E. and Soumelis, V. (2008). A critical function for transforming growth factor-beta, interleukin 23 and proinflammatory cytokines in driving and modulating human T(H)-17 responses. Nat Immunol **9**(6): 650-657.
- Voo, K. S., Wang, Y. H., Santori, F. R., Boggiano, C., Wang, Y. H., Arima, K., Bover, L., Hanabuchi, S., Khalili, J., Marinova, E., Zheng, B., Littman, D. R. and Liu, Y. J. (2009). Identification of IL-17-producing FOXP3⁺ regulatory T cells in humans. Proc Natl Acad Sci U S A **106**(12): 4793-4798.
- Vorobjova, T., Uibo, O., Heilman, K., Rago, T., Honkanen, J., Vaarala, O., Tillmann, V., Ojakivi, I. and Uibo, R. (2009). Increased FOXP3 expression in small-bowel mucosa of children with coeliac disease and type I diabetes mellitus. Scand J Gastroenterol **44**(4): 422-430.
- Wada, Y., Hisamatsu, T., Kamada, N., Okamoto, S. and Hibi, T. (2009). Retinoic acid contributes to the induction of IL-12-hypoproducing dendritic cells. Inflamm Bowel Dis Epub ahead of print.
- Wahl, S. M., Wen, J. and Moutsopoulos, N. (2006). TGF-beta: a mobile purveyor of immune privilege. Immunol Rev **213**: 213-227.
- Wakefield, L. M. and Roberts, A. B. (2002). TGF-beta signaling: positive and negative effects on tumorigenesis. Curr Opin Genet Dev **12**(1): 22-29.
- Walker, L. S. (2008). Natural Treg in autoimmune diabetes: all present and correct? Expert Opin Biol Ther **8**(11): 1691-1703.

- Walker, M. R., Kasprowicz, D. J., Gersuk, V. H., Benard, A., Van Landeghen, M., Buckner, J. H. and Ziegler, S. F. (2003). Induction of FoxP3 and acquisition of T regulatory activity by stimulated human CD4+CD25- T cells. *J Clin Invest* **112**(9): 1437-1443.
- Wang, J., Ioan-Facsinay, A., van der Voort, E. I., Huizinga, T. W. and Toes, R. E. (2007). Transient expression of FOXP3 in human activated nonregulatory CD4+ T cells. *Eur J Immunol* **37**(1): 129-138.
- Wapenaar, M. C., Monsuur, A. J., van Bodegraven, A. A., Weersma, R. K., Bevova, M. R., Linskens, R. K., Howdle, P., Holmes, G., Mulder, C. J., Dijkstra, G., van Heel, D. A. and Wijmenga, C. (2008). Associations with tight junction genes PARD3 and MAGI2 in Dutch patients point to a common barrier defect for coeliac disease and ulcerative colitis. *Gut* **57**(4): 463-467.
- Weaver, C. T., Hatton, R. D., Mangan, P. R. and Harrington, L. E. (2007). IL-17 family cytokines and the expanding diversity of effector T cell lineages. *Annu Rev Immunol* **25**: 821-852.
- Wehkamp, J., Salzman, N. H., Porter, E., Nuding, S., Weichenthal, M., Petras, R. E., Shen, B., Schaeffeler, E., Schwab, M., Linzmeier, R., Feathers, R. W., Chu, H., Lima, H., Jr., Fellermann, K., Ganz, T., Stange, E. F. and Bevins, C. L. (2005). Reduced Paneth cell alpha-defensins in ileal Crohn's disease. *Proc Natl Acad Sci U S A* **102**(50): 18129-18134.
- Weiner, H. L. (2001). Oral tolerance: immune mechanisms and the generation of Th3-type TGF-beta-secreting regulatory cells. *Microbes Infect* **3**(11): 947-954.

- Weinstock, J. V. and Elliott, D. E. (2009). Helminths and the IBD hygiene hypothesis. *Inflamm Bowel Dis* **15**(1): 128-133.
- Wildin, R. S., Ramsdell, F., Peake, J., Faravelli, F., Casanova, J. L., Buist, N., Levy-Lahad, E., Mazzella, M., Goulet, O., Perroni, L., Bricarelli, F. D., Byrne, G., McEuen, M., Proll, S., Appleby, M. and Brunkow, M. E. (2001). X-linked neonatal diabetes mellitus, enteropathy and endocrinopathy syndrome is the human equivalent of mouse scurfy. *Nat Genet* **27**(1): 18-20.
- Wilson, N. J., Boniface, K., Chan, J. R., McKenzie, B. S., Blumenschein, W. M., Mattson, J. D., Basham, B., Smith, K., Chen, T., Morel, F., Lecron, J. C., Kastelein, R. A., Cua, D. J., McClanahan, T. K., Bowman, E. P. and de Waal Malefyt, R. (2007). Development, cytokine profile and function of human interleukin 17-producing helper T cells. *Nat Immunol* **8**(9): 950-957.
- Wolf, M., Schimpl, A. and Hunig, T. (2001). Control of T cell hyperactivation in IL-2-deficient mice by CD4(+)CD25(-) and CD4(+)CD25(+) T cells: evidence for two distinct regulatory mechanisms. *Eur J Immunol* **31**(6): 1637-1645.
- Wong, C. K., Ho, C. Y., Li, E. K. and Lam, C. W. (2000). Elevation of proinflammatory cytokine (IL-18, IL-17, IL-12) and Th2 cytokine (IL-4) concentrations in patients with systemic lupus erythematosus. *Lupus* **9**(8): 589-593.
- Woywodt, A., Neustock, P., Kruse, A., Schwarting, K., Ludwig, D., Stange, E. F. and Kirchner, H. (1994). Cytokine expression in intestinal mucosal biopsies. In situ hybridisation of the mRNA for interleukin-1 beta, interleukin-6 and tumour necrosis factor-alpha in inflammatory bowel disease. *Eur Cytokine Netw* **5**(4): 387-395.

- Wurster, A. L., Rodgers, V. L., Satoskar, A. R., Whitters, M. J., Young, D. A., Collins, M. and Grusby, M. J. (2002). Interleukin 21 is a T helper (Th) cell 2 cytokine that specifically inhibits the differentiation of naive Th cells into interferon gamma-producing Th1 cells. *J Exp Med* **196**(7): 969-977.
- Xavier, R. J. and Podolsky, D. K. (2007). Unravelling the pathogenesis of inflammatory bowel disease. *Nature* **448**(7152): 427-434.
- Xu, H., Mao, Y., Dai, Y., Wang, Q. and Zhang, X. (2009). CD4CD25+ regulatory T cells in patients with advanced gastrointestinal cancer treated with chemotherapy. *Onkologie* **32**(5): 246-252.
- Xu, L., Kitani, A., Fuss, I. and Strober, W. (2007). Cutting edge: regulatory T cells induce CD4+CD25-Foxp3- T cells or are self-induced to become Th17 cells in the absence of exogenous TGF-beta. *J Immunol* **178**(11): 6725-6729.
- Yagi, H., Nomura, T., Nakamura, K., Yamazaki, S., Kitawaki, T., Hori, S., Maeda, M., Onodera, M., Uchiyama, T., Fujii, S. and Sakaguchi, S. (2004). Crucial role of FOXP3 in the development and function of human CD25+CD4+ regulatory T cells. *Int Immunol* **16**(11): 1643-1656.
- Yamamoto, T., Nakahigashi, M., Umegae, S., Kitagawa, T. and Matsumoto, K. (2005). Impact of elemental diet on mucosal inflammation in patients with active Crohn's disease: cytokine production and endoscopic and histological findings. *Inflamm Bowel Dis* **11**(6): 580-588.
- Yang, L., Anderson, D. E., Baecher-Allan, C., Hastings, W. D., Bettelli, E., Oukka, M., Kuchroo, V. K. and Hafler, D. A. (2008). IL-21 and TGF-beta are required for differentiation of human T(H)17 cells. *Nature* **454**(7202): 350-352.

Yang, X. O., Panopoulos, A. D., Nurieva, R., Chang, S. H., Wang, D., Watowich, S. S. and Dong, C. (2007). STAT3 regulates cytokine-mediated generation of inflammatory helper T cells. *J Biol Chem* **282**(13): 9358-9363.

Yang, Y., Weiner, J., Liu, Y., Smith, A. J., Huss, D. J., Winger, R., Peng, H., Cravens, P. D., Racke, M. K. and Lovett-Racke, A. E. (2009). T-bet is essential for encephalitogenicity of both Th1 and Th17 cells. *J Exp Med.*

Ye, P., Rodriguez, F. H., Kanaly, S., Stocking, K. L., Schurr, J., Schwarzenberger, P., Oliver, P., Huang, W., Zhang, P., Zhang, J., Shellito, J. E., Bagby, G. J., Nelson, S., Charrier, K., Peschon, J. J. and Kolls, J. K. (2001). Requirement of interleukin 17 receptor signaling for lung CXC chemokine and granulocyte colony-stimulating factor expression, neutrophil recruitment, and host defense. *J Exp Med* **194**(4): 519-527.

Yen, D., Cheung, J., Scheerens, H., Poulet, F., McClanahan, T., McKenzie, B., Kleinschek, M. A., Owyang, A., Mattson, J., Blumenschein, W., Murphy, E., Sathe, M., Cua, D. J., Kastelein, R. A. and Rennick, D. (2006). IL-23 is essential for T cell-mediated colitis and promotes inflammation via IL-17 and IL-6. *J Clin Invest* **116**(5): 1310-1316.

Yokoyama, A., Kohno, N., Sakai, K., Kondo, K., Hirasawa, Y. and Hiwada, K. (1997). Circulating levels of soluble interleukin-6 receptor in patients with bronchial asthma. *Am J Respir Crit Care Med* **156**(5): 1688-1691.

Youngman, K. R., Simon, P. L., West, G. A., Cominelli, F., Rachmilewitz, D., Klein, J. S. and Fiocchi, C. (1993). Localization of intestinal interleukin 1 activity and protein and gene expression to lamina propria cells. *Gastroenterology* **104**(3): 749-758.

- Yu, Q. T., Saruta, M., Avanesyan, A., Fleshner, P. R., Banham, A. H. and Papadakis, K. A. (2007). Expression and functional characterization of FOXP3+ CD4+ regulatory T cells in ulcerative colitis. *Inflamm Bowel Dis* **13**(2): 191-199.
- Zaph, C., Du, Y., Saenz, S. A., Nair, M. G., Perrigoue, J. G., Taylor, B. C., Troy, A. E., Kobuley, D. E., Kastelein, R. A., Cua, D. J., Yu, Y. and Artis, D. (2008). Commensal-dependent expression of IL-25 regulates the IL-23-IL-17 axis in the intestine. *J Exp Med* **205**(10): 2191-2198.
- Zheng, S. G. (2008). The Critical Role of TGF-beta1 in the Development of Induced Foxp3+ Regulatory T Cells. *Int J Clin Exp Med* **1**(3): 192-202.
- Zheng, S. G., Wang, J. and Horwitz, D. A. (2008). Cutting edge: Foxp3+CD4+CD25+ regulatory T cells induced by IL-2 and TGF-beta are resistant to Th17 conversion by IL-6. *J Immunol* **180**(11): 7112-7116.
- Zheng, S. G., Wang, J., Wang, P., Gray, J. D. and Horwitz, D. A. (2007). IL-2 is essential for TGF-beta to convert naive CD4+CD25- cells to CD25+Foxp3+ regulatory T cells and for expansion of these cells. *J Immunol* **178**(4): 2018-2027.
- Zheng, S. G., Wang, J. H., Gray, J. D., Soucier, H. and Horwitz, D. A. (2004). Natural and induced CD4+CD25+ cells educate CD4+CD25- cells to develop suppressive activity: the role of IL-2, TGF-beta, and IL-10. *J Immunol* **172**(9): 5213-5221.
- Zhou, L., Ivanov, II, Spolski, R., Min, R., Shenderov, K., Egawa, T., Levy, D. E., Leonard, W. J. and Littman, D. R. (2007). IL-6 programs T(H)-17 cell differentiation by promoting sequential engagement of the IL-21 and IL-23 pathways. *Nat Immunol* **8**(9): 967-974.

Zhou, L., Lopes, J. E., Chong, M. M., Ivanov, II, Min, R., Victora, G. D., Shen, Y., Du, J., Rubtsov, Y. P., Rudensky, A. Y., Ziegler, S. F. and Littman, D. R. (2008). TGF-beta-induced Foxp3 inhibits T(H)17 cell differentiation by antagonizing RORgammat function. *Nature* **453**(7192): 236-240.