
Chapter 5: General Conclusion

GENERAL CONCLUSION

The effect of quinolones on the immune system has been mainly studied *in vitro*. Despite some conflicting results due to variation in study methodologies, certain conclusions can be drawn. Clinically relevant concentrations of most of quinolones seem to have no direct effect on isolated immune parameters, such as phagocytic cell functions, lymphocyte proliferation immunoglobulin production, cytokine production and bone marrow progenitor cell proliferation. *In vivo* studies are few, and are generally in agreement with the *in vitro* findings. Only high doses administered to experimental animals caused suppressive effects, while therapeutic doses are usually not associated with measurable alterations in immune functions. Secondary anti-inflammatory properties would be clinically useful for treating acute lung injury and many chronic lung diseases.

Therefore, I conclude that moxifloxacin at therapeutically relevant concentrations does not have any direct effects, either inhibitory or stimulatory, on human leukocytes (neutrophils and lymphocytes) functions *in vitro*, but rather interacts directly with target bacteria rendering them more vulnerable to eradication by leucocytes.

Chapter 6: References

REFERENCES

- Abbas, A.K., Lichtman, A.H. and Pober, J.S. 1997. Cellular and molecular immunology (third edition). Saunders text and review series. USA. Pp.16-22.
- Al-Daccak, R., Mooney, N. and Charron, D. 2004. MHC class II signaling in antigen-presenting cells. *Curr Opin Immunol.* **16:** 108-113.
- Alon, R., Aker, M., Feigelson, S., Sokolovsky-Eisenberg, M., Staunton, D.E., Cinamon, G., Grabovsky, V., Shamri, R., and Etzioni, A. 2003. A novel genetic leukocyte adhesion deficiency in subsecond triggering of integrin avidity by endothelial chemokines results in impaired leukocyte arrest on vascular endothelium under shear flow. *Blood.* **101:** 4437-4445.
- Alonso, A., Bayon, Y., Mateos, J.J. and Sanchez Crespo, M. 1998. Signaling by leucocyte chemoattractant and Fc gamma receptors in immune-complex tissue injury. *Lab Invest.* **78:** 377-392.
- Anderson, R. 1995. The activated neutrophil: formidable forces unleashed. *SAMJ.* **85:** 1024-1028.
- Anderson, R. and Goolam Mahomed, A. 1997. Calcium efflux and influx in fMLP-activated human neutrophils are chronologically distinct events. *Clin Exp Immunol.* **110:** 132-138.
- Anderson, R., Tintinger, G.R. and Feldman, C. 2002. Regulation of calcium homeostasis in activated neutrophils and its relevance to inflammatory airway disorders. *Clin Pulm Med.* **9:** 150-156.
- Aoki, M., Ono, Y., Kunii, O. and Goldstein, E. 1994. Effect of newer quinolones on the

- extra- and intra-cellular chemiluminescence response of human polymorpho-nuclear leucocytes. *J Antimicrob Chemother.* **34:** 383-390.
- Araujo, F.G., Slifer, T.L. and Remington, J.S. 2002. Effect of moxifloxacin on secretion of cytokines by human monocytes stimulated with lipopolysaccharide. *Clin Microbiol Infect.* **8:** 26-30.
- Arredouani, A. 2004. Diversification of function and pharmacology in intracellular calcium signaling. *Cell Sci Rev.* **1:** ISSN1742-8130.
- Babior, B.M. 1999. Activation of the neutrophil respiratory burst oxidase. *J Infect Dis.* **179:** S309-S317.
- Bachmann, M.F. and Kopf, M. 2002. Balancing protective immunity and immunopathology. *Curr Opin Immunol.* **14:** 413-419.
- Bainton, D.F. 1999. Developmental biology of neutrophils and eosinophils. In: Gallin J.I. and Snyderman, R. editors. *Inflammation: Basic principles and clinical correlates.* (third edition) Lippincott Williams and Wilkins. Pp13-34.
- Ball, P. 2000. Quinolone generations: natural history or natural selection? *J Antimicrob Chemother.* **46:** 17-24.
- Balsinde, J. and Balboa, M.A. 2005. Cellular regulation and proposed biological functions of group v calcium-independent phospholipase A₂ in activated cells. *Cell Signalling.* **17:** 1052-1062.
- Bank, U., Kupper, B., Reinhold, D., Hoffmann, T. and Ansorge, S. 1999. Evidence for a critical role of neutrophil-derived serine proteases in the inactivation of IL-6 at site of inflammation. *FEBS Lett.* **461:** 235-240.

- Beatty, K., Robertie, P., Senior, R.M. and Travis, J. 1982. Determination of oxidized alpha-1-proteinase inhibitor in serum. *J Lab Clin Med.* **100:** 186-192.
- Bearden, D.T. and Danziger, L.H. 2001. Mechanism of action and resistance to Quinolones. *Pharmacother.* **21:** 2245-2325.
- Ben-Baruch, A. 2006. Inflammation-associated immune suppression in cancer: the role played by cytokine, chemokines and additional mediators. *Semin Cancer Biol.* **16:** 38-52.
- Berridge, M.J., Lipp, P. and Bootman, M.D. 2000. The versatility and universality of calcium signaling. *Nat Rev Mol Cell Biol.* **1:** 11-21.
- Blattman, J.N., Grayson, Jm., Wherry, E.J., Kaech, S.M., Smith, K.A. and Ahmed, R. 2003. Therapeutic use of IL-2 to enhance antiviral T-cells responses *in vivo*. *Nat Med.* **9:** 540-547.
- Bolotina, V.M. 2004. Store-operated channels: diversity and activation mechanisms. *Sci STKE.* **243:** p34.
- Borregaard, E. and Cowland, J.B. 1997. Granules of the human neutrophilic polymorphonuclear leukocyte. *Blood.* **89:** 3503-3521.
- Butz, E.A. and Bevan, M.J. 1998. Massive expansion of antigen-specific CD8⁺ T cells during an acute virus infection. *Immunity.* **8:** 167-175.
- Caeiro, J-P. and Lannini, P.B. 2003. Moxifloxacin (Avelox®): a novel fluoroquinolone with a broad spectrum of activity. *Exp Rev Anti-infect Ther.* **1:** 363-370.
- Cassatella, M.A. 1999. Neutrophil-derived proteins: selling cytokines by the pound. *Adv Immunol.* **73:** 369-409.

- Cham, B.P., Gerrad, J.M. and Bainton, D.F. 1994. Granulophysin is located in the membrane of azurophilic granules in human neutrophils and mobilizes to the plasma membrane following cell stimulation. *Am J Path.* **144:** 1369-1380.
- Cheng, L.E., öhlén, C., Nelson, B. H. and Greenberg, P.D. 2002. Enhanced signaling through the IL-2 receptor in CD8⁺ T-cells regulated by antigen recognition results in preferential proliferation and expanding CD8⁺ T-cells rather than promotion of cell death. *PNAS.* **99:** 3001-3006.
- Choi, J., Song, M., Kim, S., Lee, D., Yoo, J. and Shin, W. 2003. Effect of moxifloxacin on production of proinflammatory cytokines from human peripheral blood mononuclear cells. *Antimicrob Agents Chemother.* **47:** 3704-3707.
- Cockeran, R., Theron, A.J., Steel, H.C., Matlola, N.M., Mitchell, T.J. Feldman, C. and Anderson, R. 2001. Pro-inflammatory interactions of pneumolysin with human neutrophils. *J Infect Dis.* **183:** 604-611.
- Cockeran, R., Anderson, R. and Feldman, C. 2002. The role of pneumolysin in the pathogenesis of *Streptococcus pneumoniae* infection. *Curr Opin Infect Dis.* **15:** 235-239.
- Cockeran, R., Anderson, R. and Feldman, C. 2003. Pneumolysin in the immunopathogenesis and treatment of pneumococcal disease. *Expert Rev Anti-infect Ther.* **1:** 231-239.
- Coelho, A.L., Hogaboam, C.M. and Kunkel, S.L. 2005. Chemokines provide the sustained inflammatory bridge between innate and acquired immunity. *Cytokine Growth Fact Rev.* **16:** 553-560.
- Collins, D.P. 2000. Cytokine and cytokine receptor expression as a biological indicator of

- immune activation: important considerations in the development of in vitro model systems. *J Immunol Meth.* **243:** 125-145.
- Cooper, N.R. 1999. Biology of the complement system. In: Gallin J.I. and Snyderman, R. editors. *Inflammation: Basic principles and clinical correlates.* (third edition) *Lippincott Williams and Wilkins.* Pp218-315.
- Corbett, E. F. and Michalak, M. 2000. Calcium signalling molecule in the endoplasmic reticulum. *Trends Biochem Sci.* **25:** 307-311.
- Dalhoff, A. and Shalit, I. 2003. Immunomodulatory effects of quinolones. *Lancet Infect Dis.* **3:** 359-371.
- Dalhoff, K., Hansen, F., Dromann, D., Schaaf, B., Aries, S.P. and Braun, J. 1998. Inhibition of neutrophil apoptosis and modulation of the inflammatory response by granulocyte colony-stimulating factor in healthy and ethanol-treated human volunteers. *J Infect Dis.* **178:** 891-895.
- DeLeo, F.R. and Quinn, M.T. 1996. Assembly of the phagocyte NADPH oxidase: molecular interaction of oxidase proteins. *J Leuk Biol.* **60:** 677-691.
- Del Pozo, M.A., Sanchez-Mateos, P., Nieto., M. and Sanchez-Madrid, F. 1995. Chemokines regulate cellular polarization and adhesion receptor redistribution during lymphocyte interaction with endothelium and extracellular matrix. Involvement of cAMP signaling pathway. *J Cell Biol.* **131:** 495-508.
- Dolmetch, R.E., Lewis, R.S., Goodnow, C.C. and Healy, J.I. 1997. Differential activation of transcription factors induced by Ca²⁺ response amplitude and duration. *Nature.* **386:** 855-858.
- Dorfman, J.R. and Germain, R.N. 2002. MHC-dependent survival of naïve T cells - A

- complicated answer to a simple question. *Microbe Infect.* **4:** 547-554.
- Drlica, K. 1999. Mechanism of fluoroquinolone action. *Curr Opin Microbiol.* **2:** 504-508.
- Driver, I. 2004. Increased affinity of IL-2 ligand to the IL-2 α -receptor leads to increased ligand persistence and cell growth. *MURJ Reports*, V11.
- Dröge, W. 2002. Free radicals in the physiological control of cell function. *Physiol Rev.* **82:** 47-95.
- Duncan, K. 2003. Progress in TB drug development and what is still needed. *Tubercul.* **83:** 201-207.
- Duncan, K. and Barry, C.E. 2004. Prospects for new antitubercular drugs. *Curr Opin Microbiol.* **7:** 460-465.
- Dustin, M. and Cooper, J. 2000. The immunological synapse and the actin cytoskeleton: molecular hardware for T cell signaling. *Nature Immunol.* **1:** 23-30.
- Ellery, J.M. and Nicholls, P.J. 2002. Alternate signaling pathways from the IL-2 receptor. *Cytokines Growth fact Rev.* **13:** 27-40.
- Favre, C.J., Nüsse, O., Lew, D.P. and Krause, K-H. 1996. Store-operated Ca²⁺ influx: what is the message from the stores to membrane? *J Lab Clin Med.* **128:** 19-26.
- Feghali, C.A. and Wright, T.M. 1997. Cytokines in acute and chronic inflammation. *Front Biosci.* **2:** 12-26.
- Fischer, S. and Adam, D. 2001. Effects of moxifloxacin on neutrophil phagocytosis, burst production, and killing as determined by a whole-blood cytofluorometric method. *Antimicrob Agents Chemother.* **45:** 2668-2669.

- Fournier, B. and Hooper, D.C. 1998. Mutations in topoisomerase IV and DNA gyrase of *Staphylococcus aureus*: novel pleiotropic effects on quinolone and coumarin activity. *Antimicrob Agents Chemother.* **42:** 121-128.
- Gaffen, S.L. 2001. Signaling domains of the IL-2R. *Cytokines.* **14:** 63-77.
- Gaffen, S.L. and Liu, K.D. 2004. Overview of IL-2 function, production and clinical applications. *Cytokines.* **28:** 108-123.
- Galley, H.F., Dhillon, J.K., Paterson, R.L. and Webster, N.R. 2000. Effects of ciprofloxacin on the activation of the transcription factors nuclear factor κB, activator protein-1 and nuclear factor IL-6, and IL-6 and IL-8 mRNA expression in human endothelial cell line. *Clin Sci.* **99:** 405-410.
- Garcia-Sancho, J. 2000. SOC and unSOC. *News Physiol Sci.* **15:** 159-160.
- Geiszt, M., Kapus, A., Német K., Truett III, A.P. and Murray, J.J. 1997. Phosphatase activity regulates superoxide anion generation and intracellular signaling in human neutrophils. *Biochim Biophys Acta.* **1336:** 243-253.
- Gerard, C. and Rollins, B.J. 2001. Chemokines and disease. *Nat Immunol.* **2:** 108-115.
- Gilat, D., Chalon, L., Hershkoviz, R. and Lider, O. 1996. Counter-interactions between tissue-infiltrating T lymphocytes, pro-inflammatory mediators, and enzymatically-modified extracellular matrix. *Immunol Today.* **17:** 16-21.
- Gimenes, V.M.F., de Souza, M.D.G., Ferreira, K.S., Marques, S.G., Gonçalves, A.G., Santos, D.V.C.L., Silva, C.M.P. and Almeida, S.R. 2005. Cytokine and lymphocyte proliferation in patients with different clinical forms of chromoplastomycosis. *Microb Infect.* **7:** 708-713.

- Gosling, R.D., Uiso, L.O., Sam, N.S., Borgard, E., Kanduma, E.G., Nyindo, M., Morris, R.W. and Gillespie, S.H. 2003. The bactericidal activity of moxifloxacin in patients with pulmonary tuberculosis. *Am J Respir Crit Care Med.* **168:** 1342-1345.
- Gouwy, M., Struyf, S., Proost, P. and van Damme, J. 2005. Synergy in cytokine and chemokine networks amplifies the inflammatory response. *Cytokine Growth Factor Rev.* **16:** 561-80.
- Hale, L.P. and Haynes, B.F. 1999. Overview of development and function of lymphocytes. In: Gallin J.I. and Snyderman, R. editors. *Inflammation: Basic principles and clinical correlates* (third edition). *Lippincott Williams and Wilkins. Philadelphia* p119-135.
- Hall, I.H., Schwab U.E., Ward, E.S. and Lves, T.J. 2003. Effect of moxifloxacin in zymogen A or *S. aureus* stimulated human THP-1 monocytes on the inflammatory process and the spread of infection. *Life Sci.* **73:** 2675-2685.
- Hallett, M.B. 2003. Holding back neutrophil aggression the oxidase has potential. *Clin. Exp Immunol.* **132:**181-184.
- Hashemi, B.B., Penkala, J.E., Vens, C., Huls, H., Cubbage, M. and Sams, C.F. 1999. T-cell activation response are differentially regulated during clinorotation and spaceflight. *FASEB J.* **13:**2071-2081.
- Hickling, J.K. 1998. Measuring human T-lymphocyte functions. *Exp Rev Mol Med.* 13 October, Available from <http://www.expertreviews.org/jhc/txtoojhc.htm>.
- Hirayama, A., Noronha-Dutra, A.A., Gorge, M.P., Neild, G.H. and Hothersall, J.S. 2000. Inhibition of neutrophil superoxide production by uremic concentrations of guanido compounds. *J Am Sci Nephrol.* **11:** 684-689.

- Hooper, C. 1999. Mechanisms of quinolone resistance. *Drug Resist Update*. **2**: 38-55.
- Hosono, M., de Beer, O.J., van der Wal, A.C., van der Loos, C.M., Teeling, P., Piek, J.J., Ueda, M. and Beeke, A.E. 2003. Increased expression of T-cell activation marker (CD25, CD26, CD60L and CD69) in atherectomy specimens of patients with unstable angina and acute myocardial infarction. *Atherosclerosis*. **168**: 73-80.
- Hudrisier, D. and Bongrand, P. 2002. Intracellular transfer of antigen-presenting cell determinants onto T-cells: molecular mechanisms and biological significance. *FASEB J.* **16**: 477-486.
- Hunt, A.E., Lali, F.V., Lord, J.D., Nelson, B.H., Mayazaki, T., Tracey, K.J. and Foxwell, B.M.J. 1999. Role of IL-2R β -chain subdomains and Shc in p38 mitogen-activated protein (MAP) Kinase and p54 MAP kinase (stress-activated protein kinase/c-Jun N-terminal kinase) activation. *J Biol Chem*. **274**: 7591-7597.
- Internet. Available from: http://www.vetmed.wsu.edu/research_vmp/itp/ [Accessed 31 August, 2006].
- Jabs, C. M., Ferrell, J.W. and Robb, J.H. 1997. Microdetermination of plasma ATP and creatine phosphate concentrations with a luminescence biometer. *Clin Chem*. **23**: 2254-2257.
- Janeway, C.A., Travers, P., Walport, M. and Shlomchik, M.J. 2001. Immunology: the immune system in health and disease. 5th edition. *Garland USA*, pp313-315.
- Jankowski, A. and Grinstein, S. 1999. A noninvasive fluorimetric procedure for measurement of membrane potential-quantification of the NADPH oxidase-induced depolarization in activated neutrophils. *J Biol Chem*. **274**: 26098-26104.

- Ji, B., Lounis, N., Maslo, C., Truffort-Pernot, C., Bonnfous, P. and Grosset, J. 1998. *In vitro* and *in vivo* activities of moxifloxacin and ciprofloxacin against *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother.* **42:** 2066-2069.
- Katagiri, K., Hattori, M., Minato, M. and Kinashi, T. 2002. Rap1 functions as a key regulator of T-cell and antigen-presenting cell interactions and modulates T-cell responses. *Mol Cell Biol.* **22:** 1001-1015.
- Kawabata, K., Hagio, T. and Matsuoka, S. 2002. The role of neutrophil elastase in acute lung injury. *Eur J Pharmacol.* **451:** 1-10.
- Kaufmann, S.H.E. and Schaible, U.E. 2005. Antigen presentation and recognition in bacterial infections. *Curr Opin Immunol.* **17:** 79-87.
- Khan, A.A., Slifer, T.R. and Remington, J.S. 1998. Effect of Trovafloxacin on production of cytokines by human monocytes. *Antimicrob Agents Chemother.* **42:** 1713-1717.
- Kim, C. and Dinauer, M.C. 2001. Rac2 is an essential regulator of neutrophil nicotinamide adenine dinucleotide phosphate oxidase activation in response to specific signaling pathways. *J Immunol.* **166:** 1223-1232.
- Kishii, R., Takie, M., Fukuda, H., Hayashi, K. and Hosaka, M. 2003. Contribution of the 8-methoxy group to the activity of gatifloxacin against type II topoisomerase of *Streptococcus pneumoniae*. *Antimicrob Agents Chemother.* **47:** 77-81.
- Koppenol, W.H. 1998. The basic chemistry of nitrogen monoxide and peroxynitrite. *Free Radic Biol Med.* **25:** 385-391.

- Korkmaz, B., Attucci, S., Jourdan, M.L., Juliano, L. and Gauthier, F. 2005. Inhibition of neutrophil elastase by alpha 1-protease inhibitor at the surface of human polymorphonuclear neutrophils. *J Immunol.* **175:** 3329-3338.
- Kurabayashi, F., Nunoi, H., Wakamatsu, K., Tsunawaki, S., Sato, K., Ito, T. and Sumimoto, H. 2002. The adaptor protein p40^{phox} as a positive regulator of the superoxide-producing phagocyte oxidase. *EMBO J.* **21:** 6312-6320.
- Labro, M.J., el Benna, J.E. and Abdelghaffar, H. 1993. Modulation of human polymorphonuclear neutrophil function by macrolides. *J Antimicrob Chemother.* **31 Suppl C:** 51-64.
- Labro, M.J. 2000. Interference of antibacterial agents with phagocyte functions: "Immunomodulation or Immuno-fairy tales"? *Clin Micro Rev.* **13:** 615-650.
- Laing, K.J. and Secombes, C.T. 2004. Chemokines. *Dev Compar Immunol.* **28:** 443-460.
- Lanzavecchia, A., Lezzi, G. and Vida, A. 1999. From TCR engagement to T cell activation: A kinetic view of T cell behavior. *Cell.* **96:** 1-4.
- Le Cabec, V., Cowland, J.B., Calfat, J. and Borregaard, N. 1996. Targeting of proteins to granule subsets is determined by timing and not by sorting: the specific granule protein NGAL is localized to azurophilic granules when expressed in HL-60 cells. *Proc Natl Acad Sic USA.* **93:** 6454-6457.
- Lee, W.L. and Downey, G.P. 2001. Leukocyte elastase physiological functions and role in acute lung injury. *Am J Respir Crit Med.* **164:** 896-904.
- Leto, T.L. 1999. The respiratory burst oxidase. In: Gallin J.I. and Snyderman, R. editors. Inflammation: Basic principles and clinical correlates. (third edition) *Lippincott Williams and Wilkins. Philadelphia.* p769-786.

- Levine, C., Hiasa, H. and Marianas, K.J. 1998. DNA gyrase and topoisomerase IV: Biochemical activities, Physiological roles during chromosome replication and drug sensitivities. *BBA*. **1400**: 29-43.
- Li, Y., Zhu, H., Kuppusamy, P., Roubaud, V., Zweier, J. L. and Trush, M.A. 1998. Validation of lusigenin (Bis-N-methylacridinium as a chemilumigenic probe for detecting superoxide anion radical production by enzymatic systems. *J Biol Chem*. **273**: 2015-2023.
- Liao, X-L., Luo, B., Ma, J. and Wu, M-P. 2005. Neutrophils activation can be diminished by apolipoprotein A-1. *Life Sci*. **77**: 325-335.
- Linn, C.L. and Gafka, A.C. 2001. Modulation of a voltage-gated calcium channel linked to activation of glutamate receptors and calcium-induced calcium release in the catfish retina. *J Physiol*. **535**: 47-63.
- Lord, J.D., McIntosh, B.C., Greenbreg, P.D. and Nelson, B.H. 1998. The IL-2R promotes proliferation, bcl-2 and b'cl-x induction, but not cell viability through the adapter molecule Shc. *J Immunol*. **161**: 4627-4633.
- Lucas, R.L., Alves, M., del Olmo, E., San Feliciaria, A. and Payá, M. 2003. LAAE-14, a new *in vitro* inhibitor of intracellular mobilization, modulates acute and chronic inflammation. *Biochem Pharmacol*. **65**: 1539-1549.
- Ludányi, K., Nagy, Z.S., Alexa, M., Reichert, U., Michel, S., Fésüs, L. And Szandy, Z. 2005. Ligation of RAR γ inhibits proliferation of phytohaemagglutinin-stimulated T-cells via down-regulating JAK3 protein levels. *Immunol Letters*. **98**: 103-113.
- Lundqvist-Gustafsson, H., Gustafsson, M. and Dahlgren, C. 2000. Dynamic Ca²⁺ changes in neutrophil phgosome - A source for intracellular Ca²⁺ during phagolysosome formation? *Cell Calcium*. **27**: 353-362.

- Machaca, K. and Hartzell, H.C. 1999. Reversible Ca²⁺ gradients between the subplasmalemma and cytosol differentially active Ca-dependent Cl currents. *J Gen Physiol.* **113:** 249-266.
- Manjunath, N., Shankar, P., Wan, J., Weninger, W., Crowley, M.A., Hieshima, K., Springer, TA., Fan, X., Shen, H., Lieberman, J. and von Andrian, U.H. 2001. Effector differentiation is not prerequisite for generation of memory cytotoxic T lymphocytes *J Clin Invest.* **108:** 871-178.
- Marians, K. and Hiasa, H. 1997. Mechanism of quinolone action: a drug-induced structural perturbation of the DNA precedes strand cleavage by topoisomerase IV. *J Biol Chem.* **272:** 9401-9409.
- Mayer-Scholl, A., AverHoff, P. and Zychlinsky, A. 2004. How do neutrophils and pathogen interact? *Curr Opin Microb.* **7:** 62-66.
- Minkenberg, I. and Feber, E. 1984. Luciferin-dependent chemiluminescence as a new assay for NADPH-oxidase activity in particulate fractions of human polymorphonuclear leukocytes. *J Immunol Methods.* **71:** 61-67.
- Miyazaki, E., Miyazaki, M., Chen, J.M., Chaisson, R.E. and Bishai, W.R. 1999. Moxifloxacin (BAY12-8039), a new 8-methoxyquinolone is active in a mouse model of tuberculosis. *Antimicrob Agents Chemother.* **43:** 85-89.
- Mosmann, T.R. and Sad, S. 1996. The expanding universe of T-cell subsets: Th1, Th2 & more. *Immunol. Today.* **17:** 138-146.
- Nathan, C. and Sporn, M. 1991. Cytokines in context. *J Cell Biol.* **113:** 981-986.

- Nelson, B.H., Lord, J.D., Greenberg, P.D. 1996. A membrane-proximal region of the Interleukin-2 receptor gamma c chain sufficient for Jack Kinase activation and induction of proliferation in T-cells. *Mol Cell Biol.* **16:** 309-317.
- Nüsse, O., Serrander, L., Foyouzi-Yousseti, R., Monod, A., Lew, D.P. and Kause, K-H. 1997. Store-operated Ca^{2+} influx and stimulation of exocytosis in HL-60 granulocytes. *J Biol Chem.* **272:** 28360-28367.
- Niwa, M., Kanamori, Y., Hotta, K., Matsuno, H., Kozawa, O., Fujimoto, S. and Uematsu, T. 2002. Priming by grepafloxacin on cytokine production *in vivo*. *J Antimicr Chemother.* **46:** 91-94.
- Ohlsson, K. and Olsson, I. 1974. The natural poteases of human granuloctes isolation and partial characterization of granulocysts elastase. *Eur J Biochem.* **42:** 519-527.
- Ono, Y., Ohmoto, Y., Ono, K., Sakoda, Y. and Murata, K. 2000. Effects of grepafloxacin on cytokine production *in vitro*. *J Antimicrob Chemother.* **46:** 91-94.
- Oommen, J., Steel, H.C., Theron, A.J. and Anderson, R. 2004. Investigation into the relationship between calyculin A mediated potentiation of NADPH oxidase activity and inhibition of store-operated uptake of calcium by human neutrophils. *Biochem Pharmacol.* **68:** 1721-1728.
- Opal, M.S. and Depalo, V.A. 2000. Anti-inflammatory cytokines. *Chest.* **117:** 1162-1172.
- Owen, C.A., Campbell, A..M. Boukedes, S.S. and Campbell, E.J. 1997. Cytokines regulate membrane bound leukocyte elastase on neutrophils: a novel mechanism for effector activity. *Am J Physiol.* **272:** L385-393.
- Owens, R.C.J., Ebert, S.C. and Tolzis, P. 2000. New product bulletin on aveloxTM (moxifloxacin). *Am Pharmacol Assoc.* p 1-9.

- Oxenhandler, R.W., McCune, R., Subtelney, A., Truelove, C, and Tyrer, H.W. 1984. flow cytometric determination of estrogen receptors in intact cells. *Cancer Res.* **44:** 2516-2523.
- Pahlavani, M.A. 1998. T-cell signalling: effect of age. *Frontiers Biosci.* **3:** d1120-1133.
- Patterson, R.L. and van Rossum D.B. 1999. Store-operated Ca²⁺ entry: evidence for a secretion-like coupling model. *Cell.* **98:** 487-499.
- Patti, K. and Banting, G. 2004. Ins(1,4,5) P₃ metabolism and the family of IP₃-Kinases. *Cellular Signalling.* **16:** 643-654.
- Pecht, I. and Gakamsky, D.M. 2005. Spatial coordination of CD8 and TCR molecules controls antigen recognition by CD8+ T-cells. *FEBS Lett.* **579:** 3336-3341.
- Pestova, E., Millichap, J.I. Noskim, G.A. and Peterson L.R. 2000. Intracellular targets of moxifloxacin: A comparison with other fluoroquinolones. *J Antimicr chemother.* **45:** 583-590.
- Pettit, E.J. and Hallet, M.B. 1996. Localized and cytosolic calcium changes in neutrophils during engagement of CD11b/CD18 integrin visualized using confocal laser scanning reconstruction. *J Cell Sci.* **109:** 1689-1694.
- Prabhakar, U., Eirikis, E., Reddy, M., Silvestro, E., Spitz, S., Pendley II, C., Davis, HM. and Miller, B.E. 2004. Validation and comparative analysis of a multiplexed assay for the simultaneous quantitative and measurement of Th1/Th2 cytokines in human serum and human peripheral blood mononuclear or cell culture supernatants. *J Immunol Meth.* **291:** 27-38.

- Rachmilewitz, J. and Lanzavecchia, A. 2002. A temporal and spatial summation model for T-cell activation: Signal integration and antigen decoding. *Trends Immunol.* **23:** 592-595.
- Rada, B.K., Geiszt, M., van Bruggen, R., Német, K., Roos, D. and Ligeti, E. 2003. Calcium signaling is altered in myeloid cells with a deficiency in NADPH oxidase activity. *Clin Exp Immunol.* **132:** 53-60.
- Ramafi, G., Anderson, R., Theron, A.J., Feldman, C., Taylor, G.W., Wilson, R. and Cole, P.J. 1999. Exposure of N-formyl-L-methionyl-L-leucyl-L-phenylalanine-activated human neutrophils to *Pseudomonas aeruginosa* derived pigment 1-hydroxyphenazine is associated with impaired calcium efflux and potentiation of primary granule enzyme released. *Infect Immunol.* **67:** 5157-5162.
- Ramos C.L., Pou S., Brrigan B.E., Cohen M.S. and Rosen G.M. 1992. Spin trapping evidence for myeloperoxidase-dependent hydroxyl radical formation by human neutrophils and monocytes. *J Biol Chem.* **267:** 8307-8312.
- Reddy, M., Eirikis, C., Davis, C., Davis, H.M. and Prabhakar, U. 2004. Comparative analysis of lymphocyte activation marker expression and cytokine secretion profile in stimulated human peripheral blood mononuclear cell cultures: an in vitro model to monitor immune function. *J Immunol Methods.* **293:** 127-142.
- Reeves, E.P., Lu, H., Jacobs, H.L., Messina, C.G.M., Bolsover,S., Gabella,G., Potma, E.O., Warley, A., Roes, J. and Segal, A.W. 2002. Killing activity of neutrophils is through activation of protease by K⁺ flux. *Nature.* **416:** 291-297.
- Roos, D., van Bruggen, R and Meischl, C. 2003. Oxidative killing of microbes by neutrophils. *Microbes infect.* **5:** 1307 – 1315.

- Rot, A. and von Andrian, U.H. 2004. Chemokines in innate and adaptive host defense: basic chemokine grammar for immune cells. *Ann. Rev Immunol.* **2**: 891-928.
- Sallusto, F., Mackay, C.R. and Lanzavecchia, A. 2000. The role of chemokine in primary, effector, and memory immune responses. *Annu Rev Immunol.* **18**: 593-620.
- Schrenzel, J., Serrander, L., Banfi, B., Nusse, O., Fouyouzi, R., Lew, D.P., Demaurex, N. and Krause, K-H. 1998. Electron currents generated by the human phagocyte NADPH oxidase. *Nature*. **392**: 734-737.
- Segal, B.H., Leto T.L. Gallin J.I. Malech H.I. and Holland S.M. 2000. Genetic, biochemical and clinical features of chronic granulomatous disease. *Medicine*. **79**: 170-200.
- Seguchi, H. and Kobayashi, T. 2002. Study of NADPH oxidase-activated sites in human neutrophils. *J Elect Microsc.* **51**: 87-91.
- Sewell, A.K., Gerth, U.C., Price, D.A., Purbhoo, M.A., Boulter, J.M., Gao, G.F., Bell, J.I., Phillips, R.E. and Jakobsen, B.K. 1999. Antagonism of cytotoxic T-lymphocyte activation by soluble CD8. *Nature Med.* **5**: 399-404.
- Shalit, I., Horev-Azaria, L., Fabian, I., Blau, H., Kariv, N., Shechtman, I., Alteraz, H. and Kletter, Y. 2002. Immunomodulatory and protective effects of moxifloxacin against *Candida albicans*-induced bronchopneumonia in mice injected with cyclophosphamide. *Antimicr Agents Chemother.* **46**: 2442-2449.
- Sharfe, N., Dadi, H.K., Shahar, M. and Roifman, C.M. 1997. Human immune disorder arising from mutation of the α chain of the IL-2R. *Proc Natl Acad Sci USA*. **94**: 3168-3171.

- Shaw, A.S. and Dustin, M.L. 1997. Making the T-cell receptor go the distance: a topological view of the T-cell activation. *Immun.* **6:** 361-369.
- Shiose, A. and Sumimoto, H. 2000. Arachidonic acid and phosphorylation synergistically induce a conformational change of p47 phox to activate the phagocyte NADPH oxidase. *J Biol Chem.* **275:** 13793-13801.
- Shimizu, Y. and Shaw, S. 1991. Lymphocyte interactions with extracellular matrix. *FASEB J.* **5:** 2292-2299.
- Stass, H., Dalhoff, A., Kubitza, D. and Schühly, U. 1999. Pharmacokinetics, safety, and tolerability of ascending single dose of moxifloxacin, administered to health subjects. *Antimicrob Agents Chemother.* **42:** 2060-2065.
- Steeber, D.A., Tang, M.L.K., Green, N.E., Zhang, X-Q., Sloane, J.E. and Tedder, T. F. 1999. Leukocyte entry into site of inflammation requires overlapping interactions between the L-selectin and ICAM-1 pathway. *J Immunol.* **163:** 2176-2186.
- Steel, H.C. and Anderson, R. 2002. Dissociation of the PAF-receptor from NADPH oxidase and adenylate cyclase in human neutrophils results in accelerated influx and delayed clearance of cytosolic calcium. *Brit J Pharmacol.* **136:** 81-89.
- Steinbeck M.J. Khan A.U. and Karnousky M.J. 1992. Intracellular singlet oxygen generation by phagocytosing neutrophils in response to particles coated with a chemical trap. *J Biol Chem.* **267:** 13425- 13433.
- Stephens, L.A. and Mason, D. 2000. CD25 is a marker for CD4⁺ thymocytes that prevent autoimmune diabetes in rats, but peripheral T-cell with this function are found in both CD25⁺ and CD25⁻ subpopulations. *J Immunol.* **15:** 3105-3110.

- Stroman, D.W., Dajcs, J.J., Cupp, G.A. and Schlech, B.A. 2005. In vitro and in vivo potency of moxifloxacin and moxifloxacin ophthalmic solution 0.5%, a new topical fluoroquinolone. *Surv Ophthalmol.* **50:** S16-31.
- Suzuki, Y., Nishio, K., Takeshita, K., Takeuchi, O., Watanabe, K., Sato, N., Naoki, K., Kudo, H., Aoki, T. and Yamaguchi, K. 2000. Effect of steroid on hyperoxia-induced ICAM-1 expression in pulmonary endothelial cells. *Am J Physiol-lung Cell Mol Physiol.* **278:** 245-252.
- Tedgui, A. and Mallat, Z. 2001. Anti-inflammatory mechanisms in the vascular wall. *Circul Res.* **88:** 877-881.
- Thelen, M. 2001. Dancing to the tune of chemokines. *Nat Immunol.* **2:** 129-134.
- Theilgard-Mönch, K., Porse, B.T. and Borregaard 2006. Systems biology of neutrophil differentiation and immune response. *Curr Opin Immunol.* **18:** 54-60.
- Tintinger, G., Steel, H.C. and Anderson, R. 2005. Taming the neutrophil: calcium clearance and influx mechanisms as novel targets for pharmacological control. *Clin Exp Immunol.* **141:** 191-200.
- Topham, M.K., Carveth, H.J., McIntyre, T. M., Prescott, S.M. and Zimmerman, G.A. 1998. Human endothelial cells regulate polymorphonuclear leukocyte degranulation. *FASEB J.* **12:** 733-746.
- Trautmann, A. and Valituti, S. 2003. The diversity of immunological synapses. *Curr Opin Immunol.* **15:** 249-254.
- Valituti, S., Muller, S., Cella, M., Padovan, E. and Lanzavacchia, A. 1995. Serial triggering of many T-cell receptors by a few peptide-MHC complexes. *Nature.* **375:** 148-151.

- Veziris, N., Truffort-Pernot, C., Aubry, A., Jarlier, V. and Lounis, N. 2003. Fluoroquinolone-containing third-line regime against mycobacterium tuberculosis in vivo. *Antimicrob Agents Chemother.* **47:** 3117-3122.
- Wang, J.C. 1996. DNA topoisomerases. *Ann Rev Biochem.* **65:** 635-692.
- Watson, R.W. O'Neill A., Brannigan A.E. Coffey, R., Marshall, J.C. Brady H.R. and Fitzpatrick J.M. 1999. Regulation of Fas antibody induced neutrophil apoptosis is both caspase and mitochondrial dependent. *FEBS Letters.* **453:** 67-71.
- Weiss T, Shalit I, Blau H, Werber S, Halperin D, Leviton A and Fabian I. 2004. Anti-inflammatory effects of moxifloxacin on activated human monocyte cells: Inhibition of NF- κ B and mitogen-activated protein kinase activation and of synthesis of proinflammatory Cytokines. *Antimicrob Agents Chemother.* **48:** 1974-1982.
- Wellmer, A., Zysk, G., Gerber, J., Kunst, T. Von Mering, M., Bunkowski, S., Eiffert, H. and Nau, R. 2002. Decreased virulence of a pneumolysin-deficient strain of streptococcus pneumoniae in meningitis. *Infect Immune.* **70:** 6504-6508.
- Werner, E. 2004. GTPases and reactive oxygen species: switches for killing and signaling, *J Cell Sci.* **117:** 143-153.
- Witko-Sarsata, V., Rieu, P., Nescamps-Latscha, B., Lesavre, P. and Halbwachs-Mecarelli, L. 2000. Biology of disease. Neutrophils: molecules, functions and pathophysiological aspects. *Lab invest.* **80:** 617-653.
- Yoshimatsu, T., Nuermberger, E., Tyagi, S., Chaisson, R., Bishai, W. and Grossset, J. 2002. Bactericidal activity of increasing daily and weekly doses of moxifloxacin in murine tuberculosis. *Antimicrob Agents Chemother.* **46:** 1875-1879.

- Zen, K. and Parkos, C.A. 2003. Leukocyte-epithelial interactions. *Curr Opin Cell Biol.* **16:** 557-564.
- Ziegler, K. and Unanué, E.R. 1981. Identification of macrophage antigen-processing event required for I-region-restricted antigen presentation to T lymphocytes. *J Immunol.* **127:** 1869-1875.