

During cellular immune stimulation, large amounts of neopterin derivatives are produced by human monocyte-derived macrophages (Figure 1) (1). Recently, neopterin production was also observed in monocyte-derived dendritic cells (2). The synthesis of neopterin is mainly stimulated by interferons and is highly specific for humans and primates based on a functional loss of the enzyme 6-pyrovoyltetrahydropterin synthase (PTPS) in these cells (3). After the first isolation of neopterin from human urine by Sakurai and Goto in 1967 (4), a



Barbara Wirleitner studied microbiology at the University of Innsbruck, Austria. She is currently working at the Institute for Medical Chemistry and Biochemistry in Innsbruck. Her research interests include the biochemical and physiological role of neopterin-derivatives in immune regulation.
barbara.wirleitner@uibk.ac.at

link between neopterin production and immune activation was first suggested after the discovery of enhanced neopterin excretion in patients with different malignant disorders and viral diseases (5). In the following studies it became obvious that neopterin concentrations measured in urine or blood reflect activation of cellular immunity. *In vivo*, a strong correlation between neopterin levels and the severity, progression, and outcome of many infectious and inflammatory diseases is found. In the last decade neopterin derivatives were revealed to exhibit distinct biochemical effects. An influence of neopterin derivatives on the activation of cellular transcription factors and interference with the cellular redox balance were reported. In this review we will focus on a potential mediatory and regulatory function of neopterin and 7, 8-dihydroneopterin in the course of inflammatory and infectious processes.

● Cellular source and synthesis of neopterin derivatives

Biosynthesis of neopterin and 7, 8-dihydroneopterin starts with guanosine 5'-triphosphate (GTP), which is cleaved by GTP-cyclohydrolase I (EC 3.5.4.16) to 7, 8-dihydroneopterin triphosphate. This compound is further converted by the two enzymes PTPS and sepiapterin reductase to 5, 6, 7, 8-tetrahydrobiopterin. Tetrahydrobiopterin is an essential

cofactor of monooxygenases of aromatic amino acids and the nitric oxide synthases. Due to a relatively low activity of the enzyme PTPS in human monocyte-derived macrophages and most possibly also in monocyte-derived dendritic cells neopterin derivatives are formed at the expense of biopterin derivatives. Thereby accumulating 7, 8-dihydroneopterin triphosphate is cleaved by phosphatases

forming neopterin and 7, 8-dihydroneopterin. In human monocyte-derived macrophages, IFN- γ is the most active stimulus of pteridine synthesis and its activity is costimulated by lipopolysaccharides (LPS) and TNF- α (1). In contrast, in monocyte-derived dendritic cells IFN- α and - β showed similar activity to induce neopterin formation as IFN- γ (2). In human urine and arterial blood samples a nearly constant ratio of neopterin: 7, 8-dihydroneopterin of 1:3 is measured, whereas a ratio of 1:2 is obtained in

serum of venous blood samples. Neopterin is constantly excreted via the kidneys, and the half-life of neopterin within the circulatory system was calculated to be approximately 90 min.

● Neopterin production during immune activation and its role as an immunodiagnostic

Neopterin concentrations in urine can be determined by high pressure liquid chromatography (HPLC) with a normal range for adults between 100 and 200 $\mu\text{mol/mol}$ creatinine. In serum, synovial fluid, saliva or cerebrospinal fluid, neopterin is measured by immunoassay. Mean serum neopterin concentrations in serum of healthy individuals lie within 5.3 ± 2.7 nM. A large number of studies show that neopterin is a reliable marker for diseases associated with activation of the cell-mediated immunity (Table 1). Neopterin measurement to estimate immune activation has big advantages compared to evaluation cytokine production such as IFN- γ due to the easy measurement procedures and the stability of the compound. Further, cytokines are more

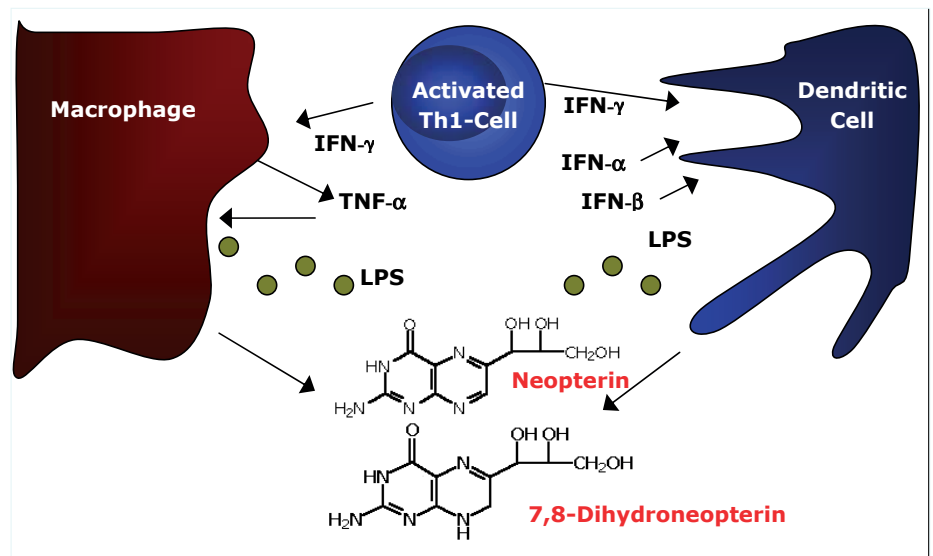


Figure 1: Production of neopterin and 7, 8-dihydroneopterin. Human and primate monocyte-derived macrophages and dendritic cells are unique to produce neopterin and 7, 8-dihydroneopterin. Main triggers for neopterin synthesis are interferon- γ (IFN- γ), tumor necrosis factor- α (TNF- α), lipopolysaccharides (LPS), IFN- α and IFN- β .

Infectious diseases	Viral infections (for example hepatitis A and B, measles, HIV-infection) (6-8) Intercellular bacteria (pulmonary tuberculosis, lepra) (9-10) Intracellular parasites (malaria, schistosomiasis mansoni) (11-12)
Allograft rejection	Solid organ transplantation (liver, pancreas, heart) (13)
Autoimmune diseases	Systemic lupus erythematosus, rheumatoid arthritis (14, 15)
Cardiac disorders	Cardiomyopathy, acute rheumatic fever, myocardial infarction (16-18)
Malignant diseases	Haematological neoplasias, gynecological malignancies, colon carcinoma (19-21)
Neurodegenerative disorders	Alzheimer's disease, Parkinson's disease (22,23)

Table 1: Diseases with increased neopterin production. Neopterin concentration in serum, urine, and other body fluids is a reliable marker for activated cell-mediated immunity. The table shows diseases with elevated neopterin concentrations.

susceptible for interaction, diffusion and synergistic effects. Increased neopterin levels in body fluids reflect extent, activity and also outcome of a large variety of diseases, including for example infections with viruses, intracellular parasites or bacteria, autoimmune disorders, malignancy and allograft rejection (Table 1).

In viral diseases, for example acute viral hepatitis A and B, elevated neopterin levels are found in body fluids already at the end of the incubation period before onset of clinical symptoms and seroconversion (6). During seroconversion, neopterin concentration declines, and values normalise after the immune response was successful to eliminate the pathogen. In chronic viral infections like human immunodeficiency virus infection (HIV), neopterin concentration declines after seroconversion, but does not normalize. During disease progression, neopterin concentrations increase with highest values when AIDS develops, paralleled by decreasing CD4+ T cells counts and correlating with viral load (8). Antiviral therapy is reflected in a decrease of neopterin production (24).

Neopterin levels are also increased in autoimmune diseases like systemic lupus erythematosus (SLE), where highest concentrations are detected in active episodes of disease (14). In patients with solid organ transplantation, daily neopterin measurement is an early detection of immunological complications such as allograft rejection or viral infections (13). In malignant diseases, correlation of neopterin levels with state of disease depends very much on the localization of the tumor. Almost 100 % of the patients with haematological neoplasias show elevated neopterin levels and a high prognostic value of the pteridine was detected (19). In contrast, only a small amount of breast cancer patients represent with increased neopterin levels (20). In line with its role as immune

activation marker, the value of neopterin measurement in malignancies does not include tumor screening, but lies in the prognosis and follow up of patients.

Neopterin measurement is also applied for blood and organ donor screenings, as activation of cellular immunity is detected at an very early time point before measurable antibody production, and neopterin production is unspecific, therefore also infections with unknown pathogens are detected. Using a cut-off limit of the 98th percentile of neopterin concentrations (= 10 nM), it is feasible to detect acute infections in blood donors with great sensitivity. As a high percentage of individuals with tumor and autoimmune diseases present with increased neopterin levels, bone and tissue graft bank-screening might be reasonable, too.

● **Biochemical and physiological functions of neopterin derivatives**

Neopterin derivatives and radicals

Since the discovery of neopterin as a marker for immune activation and its predictive value for disease progression and prognosis, many studies have been performed to evaluate a possible biochemical and physiologic function of neopterin derivatives. In activated monocyte derived macrophages, the amount of neopterin secreted correlates with hydrogen peroxide production (25). As in human monocyte-derived macrophages and dendritic cells neopterin is produced at the expense of biopterin, one could hypothesize that neopterin derivatives might replace biopterin-related functions in immune response. Tetrahydrobiopterin is an essential cofactor of the inducible nitric oxide synthase (iNOS) and thereby promoting NO production. Production of NO is known to play a role in host defence, especially upon reaction with O₂⁻ when peroxynitrite is formed (26). Therefore neopterin deriva-

tives were suspected to interfere with the cellular redox-balance. Indeed, many studies support the hypothesis that neopterin derivatives have an influence on radical formation and radical-mediated processes.

Neopterin enhances luminol-dependent chemiluminescence induced by hydrogen peroxide and chloramine-T, partly dependent on pH-value and the presence of iron ions (27). In bacterial cultures, neopterin was found to expand the anti-proliferative effect of chloramine-T, hypochlorous acid, and nitrite (28). A direct influence of neopterin on peroxynitrite formation was reported, for example the nitration of tyrosine was enhanced by neopterin and the pteridine enhanced low density lipoprotein- (LDL)-oxidation mediated by peroxynitrite (29,30). In a melanoma cell line, neopterin enhanced UV-A irradiation-induced DNA-synthesis, which was inhibited by addition of the antioxidant catalase (31). In a similar way, neopterin and other aromatic pterins increased photo-induced hydroxylation of deoxyguanosine in DNA, and the formation of pterin radicals was reported (32). In opposition to the prooxidative properties of neopterin described above, some studies describe an antioxidative effect of the pterin by inhibiting the enzymes xanthine oxidase and NADPH oxidase. Neopterin was found to suppress xanthine/xanthine oxidase induced chemiluminescence of superoxide anion (33). Further an inhibitory effect of neopterin on superoxide generation by NADPH oxidase in rodent macrophages was reported (34).

In contrast to neopterin, data on 7, 8-dihydroneopterin are concentration dependent and thus more controversial. Luminol-dependent chemiluminescence was inhibited by dihydropterins including dihydroneopterin whereas aromatic pterins acted as enhancer (35,36). Scavenging properties of 7, 8-dihydroneopterin were also described in a bacterial growth inhibition system (35). Further, oxidation of linolenic acid and LDL by amidinopropane and formation of 3-nitro-L-tyrosine by peroxynitrite were prevented by 7,8-dihydroneopterin (37). All these experiments were performed with 7,8-dihydroneopterin concentrations < 1 mM. In strict contrast, 7, 8-dihydroneopterin was shown to act as prooxidant in different experimental settings when concentrations > 1 mM were used. An enhancing effect on luminol-chemilu-

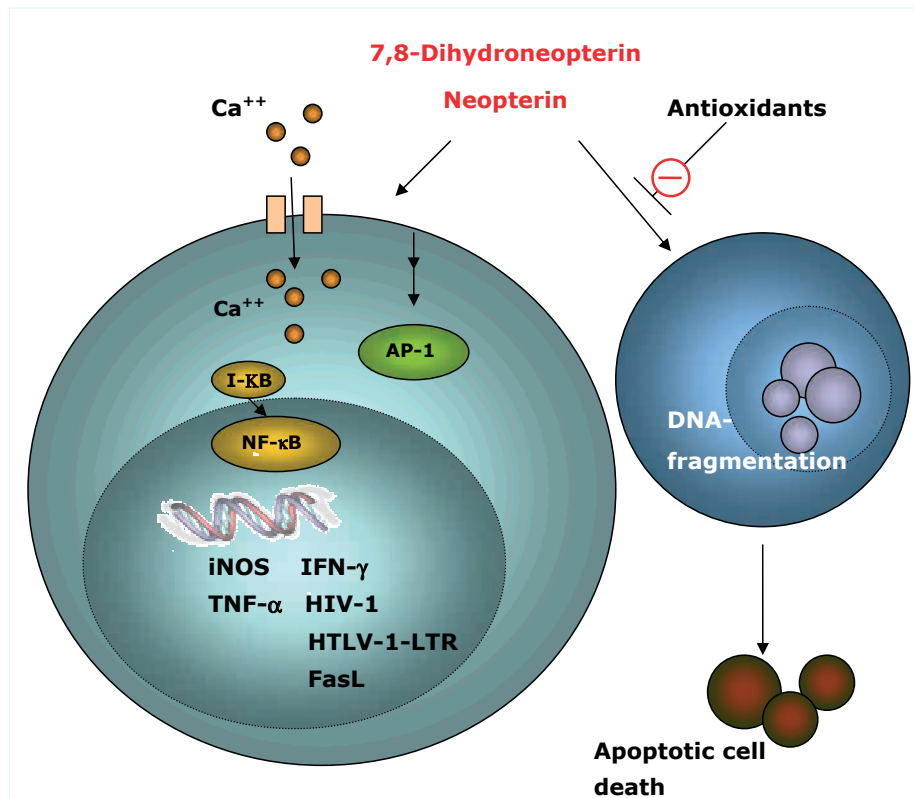


Figure 2: Signal transduction induced by neopterin-derivatives. Neopterin as well as 7, 8-dihydroneopterin induce a calcium influx in monocytoma THP-1 cells. 7, 8-Dihydroneopterin activates redox-sensitive transcription factor AP-1 and, in combination with tumor necrosis factor-α (TNF-α), also nuclear factor-κB (NF-κB) in a T lymphoblastic cell line. Rat vascular smooth muscle cells show activation of NF-κB in response to neopterin. In Jurkat cells, expression of HIV-1 promoter and HTLV-1 long terminal repeat (LTR) is enhanced by 7, 8-dihydroneopterin. Production of interferon-γ (IFN-γ) is enhanced in T lymphocytes upon treatment with 7, 8-dihydroneopterin, whereas rat vascular smooth muscle cells upregulate TNF-α formation upon incubation with neopterin. Both pteridines were found to induce apoptosis in different cell lines. Whereas neopterin particularly acted pro-apoptotic on murine alveolarepithelial cells and vascular smooth muscle cells, 7, 8-dihydroneopterin mediated apoptosis in a large variety of human cells, including T lymphocytes and neuronal cell lines.

minescence was reported with 5 mM dihydroneopterin (38). Pro-oxidative actions of 7, 8-dihydroneopterin were described in *Escherichia coli*, where the growth-inhibitory effects of hydrogen peroxide and nitrite were amplified. These findings were verified by the observation of hydroxyl radicals formation in aqueous solutions of 7, 8-dihydroneopterin, which was found also at very low levels of the pteridine (39). Authors suggested the generation of superoxide anion in the presence of 7, 8-dihydroneopterin and subsequent formation of hydrogen peroxide via the Fenton-reaction, fitting to earlier data, showing that dihydropterins reduces ferric iron to the ferrous form. In recent studies the production of oxygen free radicals in aqueous solution of pteridine-derivatives was confirmed by measuring the formation of singlet oxygen (40).

● Effects of neopterin and 7, 8-dihydroneopterin on eukaryotic cells

In the last decade intensive research focused on the action of neopterin derivatives in different cell systems (Figure 2). Neopterin as well as 7, 8-dihydroneopterin were found to induce a calcium influx in myelomonocytoma cells THP-1 (41). In contrast, neopterin inhibited the ATP-mediated calcium signal in rat alveolar epithelial cells (42). Neopterin was reported to enhance iNOS gene expression and subsequent NO release in rat vascular smooth muscle cells (VSMC) (43). It was thus suggested that neopterin might contribute to the excessive production of NO during pathophysiological hypotension in the course of sepsis. Earlier, neopterin levels were found to correlate with the severity of the disease as well as the mortality rate in septic patients (44) and synchronous augmentations in neopterin and nitrite/nitrate concentra-

tions were reported in another study (45). Neopterin also enhances nuclear uptake of nuclear factor-κB (NF-κB), a redox-sensitive transcription factor, in rat VSMC (46). In a similar way, neopterin amplifies the secretion of TNF-α from peripheral blood mononuclear cells induced by LPS, IFN-γ, and interleukin-2 (47). In VSMC, neopterin was identified as a potent stimulus of TNF-α gene expression and TNF-α protein release, providing evidence that neopterin is able to induce TNF-α synthesis as a single stimulus in non-hematopoietic cells (48). *In vivo*, the generation of TNF-α in VSMC might be important under conditions culminating in a circulatory shock reaction. The continuous presence of TNF-α in lower amounts has been connected with the fatal outcome in sepsis. The hypothesis of a potential link between neopterin and circulatory disturbances like septic shock is further supported by a study showing a decrease in coronary flow and cardiac contractility following neopterin perfusion in the Langendorff model of the rat heart (49).

In contrast to the findings cited above, cytokine-induced iNOS gene expression and NO synthesis in ovarian carcinoma cell lines was significantly suppressed following coincubation with neopterin (50). In ovarian cancer, raised neopterin levels are correlated with reduced survival (51) and the down-regulatory effect of neopterin on NO generation in these cells may inhibit apoptosis in ovarian carcinoma cells susceptible to NO. The formation of peroxynitrite from NO and O₂⁻ could play an adverse role in this process. In rat VSMC and the alveolar type II-like epithelial cell line L2, neopterin was shown to induce apoptotic cell death (52,53), although the mechanism was different in both cell lines. In L2 cells, treatment with neopterin and 7, 8-dihydroneopterin augmented TNF-α/IFN-γ-mediated apoptosis, which was not the case in VSMC. In the lymphoma cell line U937, 2h-preincubation with neopterin diminished the pro-apoptotic effect of TNF-α (38). Whereas inhibition of iNOS resulted in a strong suppression of the pro-apoptotic effects of neopterin in VSMC, no involvement of NO production on neopterin-mediated apoptosis in L2 cells was detected (53).

A time- and concentration-dependent effect of neopterin on intracellular adhesion molecule-1 (ICAM-1) gene expression and protein synthesis in type II-like alveolar epithelial cells was detected (54). Pronounced expression of ICAM-1

in the pulmonary epithelium was suggested to promote migration and activation of macrophages, neutrophils, and lymphocytes. The subsequent retention of immuno-competent cells at the site of infection might add to the damage of the airway epithelium by mediating unspecific cytotoxic host-defence reactions. Infectious diseases of the lung (e.g. sarcoidosis, lung tumors, fibrosis, adult respiratory distress syndrome) are associated with enhanced serum levels of neopterin and an increased production of ICAM-1 (55-57). A significant correlation between serum levels of neopterin and soluble ICAM-1 concentrations in the broncho-alveolar lavage fluid in patients with sarcoidosis was described (58). However, no link between neopterin production and ICAM-1 was detected in HIV-1 patients (59). In contrast, neopterin and ICAM-1 expression correlate in the acute phase of rheumatoid arthritis, suggesting that in chronic immune stimulation, shedding of the ICAM-1 molecule might occur (60). Further, production of neopterin and ICAM-1 by different cell subsets could lead to differentially compartmentalization in tissues. Macrophages within the alveolar epithelium seem to represent a source of neopterin production sufficient to interfere with ICAM-1 expression in adjacent type II cells (61).

Similar to neopterin, several studies report that 7, 8-dihydroneopterin interferes with intracellular transcription pathways. Whereas the effects of neopterin were predominantly investigated in murine cell lines, a significant effect of 7, 8-dihydroneopterin on different human cell types was found. 7,8-Dihydroneopterin enhances TNF- α induced apoptosis in human U937 cells and the combination of TNF- α with high-dose 7,8-dihydroneopterin results in the pronounced production of reactive oxygen species (ROS) (38). Consequently, application of the antioxidants N-acetylcysteine or superoxide dismutase decreased the rate of apoptosis. The pro-apoptotic actions of 7, 8-dihydroneopterin are not restricted to these cells, a number of other cell lines have been tested so far. An increased rate of apoptosis was detected in Jurkat T lymphoblasts, which was at least in part blocked by antioxidants (62,63). In a follow-up study, 7, 8-dihydroneopterin was found to induce the expression of

the Fas ligand in Jurkat T cells. Once again, this effect could be antagonized by increasing the anti-oxidative potential of the cells (64). Comparable results are documented for astrocytic, neuronal, and microglial cells (65-67). Since elevated concentrations of 7, 8-dihydroneopterin are commonly found in cerebrospinal fluid of patients with neurodegenerative diseases and central nervous system infections (68), the pteridine may contribute to the loss of neuronal cells under these conditions. In the majority of cells tested, only 7, 8-dihydroneopterin but not neopterin was effective to induce programmed cell death. Also different signal transduction molecules are triggered by 7, 8-dihydroneopterin in comparison to neopterin. In transfected Jurkat-T-lymphocytes, 7, 8-dihydroneopterin induced trans-activation of the IFN- γ -promotor as well as the type-I human T-cell leukemia virus long terminal repeat sequence and the HIV-1 promoter (62,69,70). This was further substantiated when 7, 8-dihydroneopterin was given in combination with hydrogen peroxide. The redox sensitive transcription factor AP-1 was activated by the dihydropteridine and NF- κ B activation by TNF- α was increased in the presence of 7, 8-dihydroneopterin in a lymphoblastic cell line (70). In the same cells, apoptosis induced by 7,8-dihydroneopterin was proposed to be mediated via a Bcl-2 sensitive pathway (71). In rat PC-12 cells, the pteridine activated stress activated protein kinase (SAPK) (72).

On basis of the extended research on 7, 8-dihydroneopterin-mediated apoptosis in different cell types, the influence of the pteridine on primary cultures of human T lymphocytes was tested. It was shown that freshly isolated cells obtained from healthy donors are more susceptible to undergo programmed cell death in comparison to the T lymphoblastic cell line Jurkat. Already relatively low doses of 7, 8-dihydroneopterin (200 μ M) compared to various cell lines induced elevated apoptosis rates in primary lymphocyte cultures (73). Results of T cells from healthy donors were compared with those from patients with systemic lupus erythematosus (SLE). A significantly lower rate of apoptosis was detected in lymphocytes from SLE patients, suggesting that sustained production of 7, 8-dihydroneopterin during chronic immune activation could contribute to the depletion of healthy lymphocytes and the accumulation of autoreactive cells in this diseases.

● Conclusion

In human and primates, neopterin and 7, 8-dihydroneopterin are produced during Th1-type immune stimulation primarily in response to IFN- γ , a central up-regulator of immune response. Besides its strong pro-inflammatory properties, IFN- γ was found to simultaneously induce the production of several compounds possibly involved in down-regulation of immune response in monocyte-derived macrophages and in other immuno-competent cells. In parallel to neopterin production, IFN- γ potently primes the release of ROS in monocytes/macrophages and in neutrophils (25). This process known as oxidative burst can lead to a depletion of the antioxidative capacity in tissue and the occurrence of oxidative stress. Oxidative stress can cause destruction of important cell structures such as membranes, proteins and purines (74). Production of ROI in lower concentrations can trigger redox-sensitive transcription factors and pathways in cells, and induce programmed cell death (75,76). In addition, IFN- γ is known as the main trigger for indoleamine-2,3 dioxygenase (IDO), catalyzing the conversion of tryptophan to N-formylkynurenine, leading to a locally decreased tryptophan level during inflammation. Withdrawal of tryptophan from the micro-environment suppresses growth of pathogens, intracellular replicating viruses, and uncontrolled proliferating cells (77,78). The deprivation of tryptophan during inflammation also acts on clonal expanding T cells during immune stimulation. Human monocyte-derived macrophages suppress T-cell proliferation *in vitro* via IFN- γ -mediated induction of IDO (79). Similarly, dendritic cells were reported to inhibit responsiveness of T cells to mitogenic stimulation (80). Neopterin derivatives seem to contribute to the anti-inflammatory repertoire induced by IFN- γ via modulation of the cellular redox-balance, onset of intracellular transcription factors and induction of programmed cell death. From the available data we suggest that neopterin and 7, 8-dihydroneopterin represent one of the biochemical pathways by which monocyte derived macrophages and dendritic cells down-regulate T lymphocyte activation. Especially in the state of chronic immune activation neopterin and 7, 8-dihydroneopterin might play a special role in the course of the development of immunodeficiency by depletion of T lymphocytes through induction of apoptosis.

REFERENCES

1. Huber C et al. *J Exp Med* 160, 310, 1984
2. Wirleitner B et al. *J Leukoc Biol* 72, 1148, 2002
3. Werner ER et al. *J Biol Chem* 265, 3189, 1990
4. Sakurai A et al. *J Biochem* 61, 142, 1967
5. Wachter H et al. *Hoppe Seylers Z Physiol Chem* 360, 1957, 1979
6. Reibnegger G et al. *Hepatology* 8, 771, 1988
7. Griffin DE et al. *J Infect Dis* 161, 449, 1990
8. Fuchs D et al. *Immunol Today* 9, 150, 1988
9. Hosp M et al. *Lung* 175, 265, 1997
10. Schmutzhard E et al. *East Afr Med J* 63, 577, 1986
11. Reibnegger G et al. *Trans Roy Soc Trop Med Hyg* 78, 545, 1984
12. Zwingenberger K et al. *Acta Tropica* 45, 263, 1988
13. Margreiter R et al. *Transplantation* 36, 650, 1983
14. Lim KL et al. *Ann Rheum Dis* 52, 429, 1993
15. Reibnegger G et al. *Arthritis Rheum* 29, 1063, 1986
16. Samsonov M et al. *Clin Chem* 38, 678, 1992
17. Samsonov M et al. *Clin Immunol Immunopathol* 74, 31, 1995
18. Melichar B et al. *Clin Chem* 40, 338, 1994
19. Hausen A et al. *Clin Chim Acta* 117, 297, 1981
20. Bichler A et al. *Arch Gynecol* 233, 121, 1983
21. Weiss G et al. *Cancer Res* 53, 260, 1993
22. Leblhuber F et al. *Clin Chem Lab Med* 37, 429, 1999
23. Widner B et al. *J Neural Transm* 109, 181, 2002
24. Hagberg L et al. *Scand J Infect Dis* 28, 329, 1996
25. Nathan CF *Interferon* 7, 125, 1986
26. Szabo C *Toxicol Lett* 140-141, 105, 2003
27. Murr C et al. *FEBS Lett* 338, 223, 1994
28. Wede I et al. *Free Rad Res* 31, 381, 1999
29. Herpfer I et al. *Free Radic Res* 36, 509, 2002
30. Widner B et al. *Biochem Biophys Res Commun* 248, 341, 1998
31. Kojima S et al. *Anticancer Res* 15, 1975, 1995
32. Ito K et al. *Biochemistry* 36, 1774, 1997
33. Kojima S et al. *FEBS Lett* 304, 163, 1992
34. Kojima S et al. *FEBS Lett* 329, 125, 1993
35. Weiss G et al. *FEBS Lett* 321, 89, 1993
36. Reibnegger G et al. *Free Radic Biol Med* 18, 515, 1995
37. Gieseg SP et al. *Free Radic Res* 23, 123, 1995
38. Baier-Bitterlich G et al. *FEBS Lett* 364, 234, 1995
39. Oetl K et al. *Biochem Biophys Res Commun* 234, 774, 1997
40. Thomas AH et al. *Photochem Photobiol Sci* 2, 245, 2003
41. Woll E et al. *FEBS Lett* 318, 249, 1993
42. Hoffmann G et al. *Mediators Inflamm* 11, 181, 2002
43. Schobersberger W et al. *FEBS Lett* 377, 461, 1995
44. Strohmaier W et al. *Crit Care Med* 15, 757, 1987
45. Adamik B et al. *Int Care Med* 25, 25, 1999
46. Hoffmann G et al. *FEBS Lett* 391, 181, 1996
47. Barak M et al. *Immunol Lett* 30, 101, 1991
48. Hoffmann G et al. *Int Arch Allergy Immunol* 116, 240, 1998
49. Margreiter J et al. *J Mol Cell Cardiol* 32, 1265, 2000
50. Rieder J et al. *Pteridines* 12, 140, 2001
51. Reibnegger G et al. *Cancer Res* 47, 4977, 1987
52. Hoffmann G et al. *Immunobiology* 199, 93, 1998
53. Schobersberger W et al. *FEBS Lett* 397, 263, 1996
54. Hoffmann G et al. *Clin Exp Immunol* 118, 435, 1999
55. Prior C et al. *Clin Chim Acta* 177, 211, 1988
56. Saito M et al. *Gen Pharmacol* 27, 483, 1996
57. Waydhas C et al. *Arch Surg* 127, 460, 1992
58. Baumer I et al. *Lung* 175, 105, 1997
59. Diez-Ruiz A et al. *Int Arch Allergy Immunol* 102, 56, 1993
60. Kullich W et al. *Wien Med Wochenschr* 149, 550, 1999
61. Dhondt JL et al. *Chest* 95, 348, 1989
62. Baier-Bitterlich G et al. *Oncogene* 13, 2281, 1996
63. Wirleitner B et al. *Biochem Pharmacol* 56, 1181, 1998
64. Wirleitner B et al. *Immunobiology* 203, 629, 2001
65. Enzinger C et al. *Neurochem Int* 41, 71, 2002
66. Speth C et al. *Immunobiology* 202, 460, 2000
67. Spoedt N et al. *Immunobiology* 201, 478, 2000
68. Brew BJ et al. *Ann Neurol* 28, 556, 1990
69. Baier-Bitterlich G et al. *Immunobiology* 196, 350, 1996
70. Baier-Bitterlich G et al. *AIDS Res Hum Retroviruses* 13, 173, 1997
71. Enzinger C et al. *Eur J Cell Biol* 81, 197, 2002
72. Enzinger C et al. *Neurosci Lett* 316, 157, 2001
73. Wirleitner B et al. *Cin Immunol* 107, 152, 2003
74. Halliwell B et al. *Methods Enzymol* 186, 1, 1990
75. Suzuki YJ et al. *Free Radic Biol Med* 22, 269, 1996
76. Buttke TM et al. *Free Radic Res* 22, 389, 1995
77. Pfefferkorn ER *PNAS USA* 81, 908, 1984
78. Pfefferkorn ER *Interferon Res* 6, 267, 1986
79. Munn DH et al. *J Exp Med* 189, 1363, 1999
80. Hwu P et al. *J Immunol* 164, 3596, 2000