

10 REFERENCES

- Antony, G.K., Dudek, A.Z., 2010, Interleukin 2 in cancer therapy. *Curr Med Chem* 17, 3297-3302.
- Atkinson, S., Fox, S.B., 2004, Vascular endothelial growth factor (VEGF)-A and platelet-derived growth factor (PDGF) play a central role in the pathogenesis of digital clubbing. *J Pathol* 203, 721-728.
- Bailey, W.S., 1963, Parasites And Cancer: Sarcoma In Dogs Associated With Spirocerca Lupi. *Ann N Y Acad Sci* 108, 890-923.
- Bailey, W.S., 1972, Spirocerca lupi: a continuing inquiry. *J Parasitol* 58, 3-22.
- Bailey, W.S., Cabrera, D.J., Diamond, D.L., 1963, Beetles of the family Scarabaeidae as intermediate hosts for Spirocerca lupi. *J Parasitol* 49, 485-488.
- Bazzocchi, C., Genchi, C., Paltrinieri, S., Lecchi, C., Mortarino, M., Bandi, C., 2003, Immunological role of the endosymbionts of *Dirofilaria immitis*: the Wolbachia surface protein activates canine neutrophils with production of IL-8. *Vet Parasitol* 117, 73-83.
- Betts, G., Twohig, J., Van den Broek, M., Sierro, S., Godkin, A., Gallimore, A., 2007, The impact of regulatory T cells on carcinogen-induced sarcogenesis. *Br J Cancer* 96, 1849-1854.
- Beyer, M., Schultze, J.L., 2006, Regulatory T cells in cancer. *Blood* 108, 804-811.
- Biller, B.J., Elmslie, R.E., Burnett, R.C., Avery, A.C., Dow, S.W., 2007, Use of FoxP3 expression to identify regulatory T cells in healthy dogs and dogs with cancer. *Vet Immunol Immunopathol* 116, 69-78.
- Brattig, N.W., Hoerauf, A., Fischer, P.U., Liebau, E., Bandi, C., Debrah, A., Buttner, M., Buttner, D.W., 2010, Immunohistological studies on neoplasms of female and male *Onchocerca volvulus*: filarial origin and absence of Wolbachia from tumor cells. *Parasitology* 137, 841-854.
- Brinkrolf, P., Landmeier, S., Altvater, B., Chen, C., Pscherer, S., Rosemann, A., Ranft, A., Dirksen, U., Juergens, H., Rossig, C., 2009, A high proportion of bone marrow T cells with regulatory phenotype (CD4+CD25hiFoxP3+) in Ewing sarcoma patients is associated with metastatic disease. *Int J Cancer* 125, 879-886.
- Broday, R.S., 1971, Hypertrophic osteoarthropathy in the dog: a clinicopathologic survey of 60 cases. *J Am Vet Med Assoc* 159, 1242-1256.
- Broday, R.S., 1979, Hypertrophic osteoarthropathy, In: Andrews, E.J., Ward, B.C., Altman, N.H. (Eds.) *Spontaneous Animal Models of Human Disease*. Academic Press, New York, USA, pp. 241-246.
- Broday, R.S., Thomson, R.G., Sayer, P.D., Eugster, B., 1977, Spirocerca lupi infection in dogs in Kenya. *Veterinary Parasitology* 3, 49-59.
- Carreras, J., Lopez-Guillermo, A., Fox, B.C., Colomo, L., Martinez, A., Roncador, G., Montserrat, E., Campo, E., Banham, A.H., 2006, High numbers of tumor-infiltrating FOXP3-positive regulatory T cells are associated with improved overall survival in follicular lymphoma. *Blood* 108, 2957-2964.
- Chatterjee, S.K., Zetter, B.R., 2005, Cancer biomarkers: knowing the present and predicting the future. *Future Oncol* 1, 37-50.

- Chou, P.C., Chuang, T.F., Jan, T.R., Gion, H.C., Huang, Y.C., Lei, H.J., Chen, W.Y., Chu, R.M., 2009, Effects of immunotherapy of IL-6 and IL-15 plasmids on transmissible venereal tumor in beagles. *Vet Immunol Immunopathol* 130, 25-34.
- Christie, J., Schwan, E.V., Bodenstein, L.L., Sommerville, J.E., van der Merwe, L.L., 2011, The sensitivity of direct faecal examination, direct faecal flotation, modified centrifugal faecal flotation and centrifugal sedimentation/flotation in the diagnosis of canine spirocercosis. *J S Afr Vet Assoc* 82, 71-75.
- Coomber, B.L., Denton, J., Sylvestre, A., Kruth, S., 1998, Blood vessel density in canine osteosarcoma. *Can J Vet Res* 62, 199-204.
- Correa, P., Houghton, J., 2007, Carcinogenesis of *Helicobacter pylori*. *Gastroenterology* 133, 659-672.
- Coussens, L.M., Werb, Z., 2002, Inflammation and cancer. *Nature* 420, 860-867.
- Couto, S.S., Griffey, S.M., Duarte, P.C., Madewell, B.R., 2002, Feline vaccine-associated fibrosarcoma: morphologic distinctions. *Vet Pathol* 39, 33-41.
- Craft, P.S., Harris, A.L., 1994, Clinical prognostic significance of tumour angiogenesis. *Ann Oncol* 5, 305-311.
- Curiel, T.J., Coukos, G., Zou, L., Alvarez, X., Cheng, P., Mottram, P., Evdemon-Hogan, M., Conejo-Garcia, J.R., Zhang, L., Burow, M., Zhu, Y., Wei, S., Kryczek, I., Daniel, B., Gordon, A., Myers, L., Lackner, A., Disis, M.L., Knutson, K.L., Chen, L., Zou, W., 2004, Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. *Nat Med* 10, 942-949.
- De Santo, C., Arscott, R., Booth, S., Karydis, I., Jones, M., Asher, R., Salio, M., Middleton, M., Cerundolo, V., 2010, Invariant NKT cells modulate the suppressive activity of IL-10-secreting neutrophils differentiated with serum amyloid A. *Nat Immunol* 11, 1039-1046.
- de Visser, K.E., Korets, L.V., Coussens, L.M., 2005, De novo carcinogenesis promoted by chronic inflammation is B lymphocyte dependent. *Cancer Cell* 7, 411-423.
- Di Carlo, E., Forni, G., Lollini, P., Colombo, M.P., Modesti, A., Musiani, P., 2001, The intriguing role of polymorphonuclear neutrophils in antitumor reactions. *Blood* 97, 339-345.
- Diakowska, D., Markocka-Maczka, K., Grabowski, K., Lewandowski, A., 2006, Serum interleukin-12 and interleukin-18 levels in patients with oesophageal squamous cell carcinoma. *Exp Oncol* 28, 319-322.
- Dranoff, G., 2004, Cytokines in cancer pathogenesis and cancer therapy. *Nat Rev Cancer* 4, 11-22.
- Dunn, M.E., Blond, L., Letard, D., DiFruscia, R., 2007, Hypertrophic osteopathy associated with infective endocarditis in an adult boxer dog. *Journal of Small Animal Practice* 48, 99-103.
- Dvir, E., Clift, S.J., 2010, Evaluation of selected growth factor expression in canine spirocercosis (*Spirocerca lupi*)-associated non-neoplastic nodules and sarcomas. *Vet Parasitol* 174, 257-266.
- Dvir, E., Clift, S.J., Williams, M.C., 2010, Proposed histological progression of the *Spirocerca lupi*-induced oesophageal lesion in dogs. *Vet Parasitol* 168, 71-77.

- Dvir, E., Kirberger, R.M., Malleczek, D., 2001, Radiographic and computed tomographic changes and clinical presentation of spirocercosis in the dog. *Vet Radiol Ultrasound* 42, 119-129.
- Dvir, E., Kirberger, R.M., Mukorera, V., van der Merwe, L.L., Clift, S.J., 2008, Clinical differentiation between dogs with benign and malignant spirocercosis. *Vet Parasitol* 155, 80-88.
- Dvir, E., Schoeman, J.P., Clift, S.J., McNeilly, T.N., Mellanby, R.J., 2011, Immunohistochemical characterization of lymphocyte and myeloid cell infiltrates in spirocercosis-induced esophageal nodules. *Parasite Immunol* 33, 545-553.
- Erdman, S.E., Poutahidis, T., 2010, Roles for inflammation and regulatory T cells in colon cancer. *Toxicol Pathol* 38, 76-87.
- Fitzgerald, R.C., Abdalla, S., Onwuegbusi, B.A., Sirieix, P., Saeed, I.T., Burnham, W.R., Farthing, M.J., 2002, Inflammatory gradient in Barrett's oesophagus: implications for disease complications. *Gut* 51, 316-322.
- Grencis, R.K., 2001, Cytokine regulation of resistance and susceptibility to intestinal nematode infection - from host to parasite. *Vet Parasitol* 100, 45-50.
- Grivennikov, S.I., Karin, M., 2011, Inflammatory cytokines in cancer: tumour necrosis factor and interleukin 6 take the stage. *Ann Rheum Dis* 70 Suppl 1, i104-108.
- Halper, J., 2009, Growth Factors as Active Participants in Carcinogenesis: A perspective. *Vet Pathol*.
- He, Y.X., Chen, L., Ramaswamy, K., 2002, Schistosoma mansoni, S. haematobium, and S. japonicum: early events associated with penetration and migration of schistosomula through human skin. *Exp Parasitol* 102, 99-108.
- Heimberger, A.B., Abou-Ghazal, M., Reina-Ortiz, C., Yang, D.S., Sun, W., Qiao, W., Hiraoka, N., Fuller, G.N., 2008, Incidence and prognostic impact of FoxP3+ regulatory T cells in human gliomas. *Clin Cancer Res* 14, 5166-5172.
- Heldin, C.H., Westermark, B., 1999, Mechanism of action and in vivo role of platelet-derived growth factor. *Physiol Rev* 79, 1283-1316.
- Helmby, H., Grencis, R.K., 2002, IL-18 regulates intestinal mastocytosis and Th2 cytokine production independently of IFN-gamma during *Trichinella spiralis* infection. *J Immunol* 169, 2553-2560.
- Helmby, H., Takeda, K., Akira, S., Grencis, R.K., 2001, Interleukin (IL)-18 promotes the development of chronic gastrointestinal helminth infection by downregulating IL-13. *J Exp Med* 194, 355-364.
- Herrera, L.A., Benitez-Bribiesca, L., Mohar, A., Ostrosky-Wegman, P., 2005, Role of infectious diseases in human carcinogenesis. *Environ Mol Mutagen* 45, 284-303.
- Hewitson, J.P., Grainger, J.R., Maizels, R.M., 2009, Helminth immunoregulation: the role of parasite secreted proteins in modulating host immunity. *Mol Biochem Parasitol* 167, 1-11.
- Hogg, K.G., Kumkate, S., Anderson, S., Mountford, A.P., 2003, Interleukin-12 p40 secretion by cutaneous CD11c+ and F4/80+ cells is a major feature of

- the innate immune response in mice that develop Th1-mediated protective immunity to *Schistosoma mansoni*. *Infect Immun* 71, 3563-3571.
- Hu, C.H., Hoepli, R.J.C., 1936, The migration route of *Spirocercus sanguinolenta* in experimentally infected dogs. *Chinese Medical Journal Supplement* 1, 293-311.
- Imai, H., Saio, M., Nonaka, K., Suwa, T., Umemura, N., Ouyang, G.F., Nakagawa, J., Tomita, H., Osada, S., Sugiyama, Y., Adachi, Y., Takami, T., 2007, Depletion of CD4+CD25+ regulatory T cells enhances interleukin-2-induced antitumor immunity in a mouse model of colon adenocarcinoma. *Cancer Sci* 98, 416-423.
- Itoh, H., Horiuchi, Y., Nagasaki, T., Sakonju, I., Kakuta, T., Fukushima, U., Uchide, T., Yamashita, M., Kuwabara, M., Yusa, S., Takase, K., 2009, Evaluation of immunological status in tumor-bearing dogs. *Vet Immunol Immunopathol* 132, 85-90.
- Jenkins, G.J., Mikhail, J., Alhamdani, A., Brown, T.H., Caplin, S., Manson, J.M., Bowden, R., Toffazal, N., Griffiths, A.P., Parry, J.M., Baxter, J.N., 2007, Immunohistochemical study of nuclear factor-kappaB activity and interleukin-8 abundance in oesophageal adenocarcinoma; a useful strategy for monitoring these biomarkers. *J Clin Pathol* 60, 1232-1237.
- Jones, A., Fujiyama, C., 1999, Angiogenesis in urological malignancy: prognostic indicator and therapeutic target. *BJU Int* 83, 535-555; quiz 555-536.
- Jones, M.L., 2002, Connective tissues and stains, In: Bancroft, J.D., Gamble, M. (Eds.) *Theory and practice of histological techniques*. Churchill Livingstone, Philadelphia, pp. 139-162.
- Katayama, R., Huelsmeyer, M.K., Marr, A.K., Kurzman, I.D., Thamm, D.H., Vail, D.M., 2004, Imatinib mesylate inhibits platelet-derived growth factor activity and increases chemosensitivity in feline vaccine-associated sarcoma. *Cancer Chemother Pharmacol* 54, 25-33.
- Kirpensteijn, J., Kik, M., Rutteman, G.R., Teske, E., 2002, Prognostic significance of a new histologic grading system for canine osteosarcoma. *Vet Pathol* 39, 240-246.
- Kjelgaard-Hansen, M., Goggs, R., Wiinberg, B., Chan, D.L., 2011, Use of serum concentrations of interleukin-18 and monocyte chemoattractant protein-1 as prognostic indicators in primary immune-mediated hemolytic anemia in dogs. *J Vet Intern Med* 25, 76-82.
- Kjelgaard-Hansen, M., Luntang-Jensen, M., Willesen, J., Jensen, A.L., 2007, Measurement of serum interleukin-10 in the dog. *Vet J* 173, 361-365.
- Kok, D.J., Williams, E.J., Schenker, R., Archer, N.J., Horak, I.G., 2010, The use of milbemycin oxime in a prophylactic anthelmintic programme to protect puppies, raised in an endemic area, against infection with *Spirocercus lupi*. *Vet Parasitol* 174, 277-284.
- Krzystek-Korpaczka, M., Matusiewicz, M., Diakowska, D., Grabowski, K., Blachut, K., Konieczny, D., Kustrzeba-Wojcicka, I., Terlecki, G., Banas, T., 2008, Elevation of circulating interleukin-8 is related to lymph node and distant metastases in esophageal squamous cell carcinomas--implication for clinical evaluation of cancer patient. *Cytokine* 41, 232-239.

- Lavy, E., Aroch, I., Bark, H., Markovics, A., Aizenberg, I., Mazaki-Tovi, M., Hagag, A., Harrus, S., 2002, Evaluation of doramectin for the treatment of experimental canine spirocercosis. *Vet Parasitol* 109, 65-73.
- Levine, R.A., 2002, Overexpression of the sis oncogene in a canine osteosarcoma cell line. *Vet Pathol* 39, 411-412.
- Liyanage, U.K., Moore, T.T., Joo, H.G., Tanaka, Y., Herrmann, V., Doherty, G., Drebin, J.A., Strasberg, S.M., Eberlein, T.J., Goedegebuure, P.S., Linehan, D.C., 2002, Prevalence of regulatory T cells is increased in peripheral blood and tumor microenvironment of patients with pancreas or breast adenocarcinoma. *J Immunol* 169, 2756-2761.
- London, C.A., Malpas, P.B., Wood-Follis, S.L., Boucher, J.F., Rusk, A.W., Rosenberg, M.P., Henry, C.J., Mitchener, K.L., Klein, M.K., Hintermeister, J.G., Bergman, P.J., Couto, G.C., Mauldin, G.N., Michels, G.M., 2009, Multi-center, placebo-controlled, double-blind, randomized study of oral toceranib phosphate (SU11654), a receptor tyrosine kinase inhibitor, for the treatment of dogs with recurrent (either local or distant) mast cell tumor following surgical excision. *Clin Cancer Res* 15, 3856-3865.
- Luong, R.H., Baer, K.E., Craft, D.M., Ettinger, S.N., Scase, T.J., Bergman, P.J., 2006, Prognostic significance of intratumoral microvessel density in canine soft-tissue sarcomas. *Vet Pathol* 43, 622-631.
- Maiolino, P., De Vico, G., Restucci, B., 2000, Expression of vascular endothelial growth factor in basal cell tumours and in squamous cell carcinomas of canine skin. *J Comp Pathol* 123, 141-145.
- Maizels, R.M., 2009, Parasite immunomodulation and polymorphisms of the immune system. *J Biol* 8, 62.
- Maizels, R.M., Pearce, E.J., Artis, D., Yazdanbakhsh, M., Wynn, T.A., 2009, Regulation of pathogenesis and immunity in helminth infections. *J Exp Med* 206, 2059-2066.
- Martinez-Lavin, M., 1992, Pathogenesis of hypertrophic osteoarthropathy. *Clinical & Experimental Rheumatology* 10 Suppl 7, 49-50.
- Mattarollo, S.R., Smyth, M.J., A novel axis of innate immunity in cancer. *Nat Immunol* 11, 981-982.
- Mazaki-Tovi, M., Baneth, G., Aroch, I., Harrus, S., Kass, P.H., Ben-Ari, T., Zur, G., Aizenberg, I., Bark, H., Lavy, E., 2002, Canine spirocercosis: clinical, diagnostic, pathologic, and epidemiologic characteristics. *Vet Parasitol* 107, 235-250.
- McEntee, M.C., Page, R.L., 2001, Feline vaccine-associated sarcomas. *J Vet Intern Med* 15, 176-182.
- Meeusen, E.N., 1999, Immunology of helminth infections, with special reference to immunopathology. *Vet Parasitol* 84, 259-273.
- Melendez, R.D., Suarez-Pellin, C., 2001, Spirocerca lupi and dogs: the role of nematodes in carcinogenesis. *Trends Parasitol* 17, 516; author reply 517.
- Millanta, F., Caneschi, V., Ressel, L., Citi, S., Poli, A., 2010, Expression of vascular endothelial growth factor in canine inflammatory and non-inflammatory mammary carcinoma. *J Comp Pathol* 142, 36-42.
- Mishra, A., Verma, M., 2010, Cancer Biomarkers: Are We Ready for the Prime Time? *Cancers* 2, 190-208.

- Mohammed, S.I., Craig, B.A., Mutsaers, A.J., Glickman, N.W., Snyder, P.W., deGortari, A.E., Schlittler, D.L., Coffman, K.T., Bonney, P.L., Knapp, D.W., 2003, Effects of the cyclooxygenase inhibitor, piroxicam, in combination with chemotherapy on tumor response, apoptosis, and angiogenesis in a canine model of human invasive urinary bladder cancer. *Mol Cancer Ther* 2, 183-188.
- Morroni, R., Lopez-Belmonte, J., Bazzocchi, C., Grandi, G., Kramer, L., Simon, F., 2007, Dogs with patent Dirofilaria immitis infection have higher expression of circulating IL-4, IL-10 and iNOS mRNA than those with occult infection. *Vet Immunol Immunopathol* 115, 184-188.
- Morrison, W.B., 2012, Inflammation and cancer: a comparative view. *J Vet Intern Med* 26, 18-31.
- Moss, S.F., Blaser, M.J., 2005, Mechanisms of disease: Inflammation and the origins of cancer. *Nat Clin Pract Oncol* 2, 90-97; quiz 91 p following 113.
- Mostafa, M.H., Sheweita, S.A., O'Connor, P.J., 1999, Relationship between schistosomiasis and bladder cancer. *Clin Microbiol Rev* 12, 97-111.
- Mukorera, V., Dvir, E., van der Merwe, L.L., Goddard, A., 2011a, Serum C-reactive protein concentration in benign and malignant canine spirocercosis. *J Vet Intern Med* 25, 963-966.
- Mukorera, V., Kirberger, R.M., Mabeta, P., Van der Merwe, L.L., Dvir, E., 2011b, Vascular endothelial growth factor as a marker for neoplastic transformation in canine spirocercosis. In: The 21th Congress of the European College of Veterinary Internal Medicine Companion Animals (ECVIM-CA), Seville, Spain.
- Mylonakis, M.E., Rallis, T., Koutinas, A.F., Leontides, L.S., Patsikas, M., Florou, M., Papadopoulos, E., Fytianou, A., 2006, Clinical signs and clinicopathologic abnormalities in dogs with clinical spirocercosis: 39 cases (1996-2004). *J Am Vet Med Assoc* 228, 1063-1067.
- Nieto, A., Sanchez, M.A., Martinez, E., Rollan, E., 2003, Immunohistochemical expression of p53, fibroblast growth factor-b, and transforming growth factor-alpha in feline vaccine-associated sarcomas. *Vet Pathol* 40, 651-658.
- O'Neill, K., Guth, A., Biller, B., Elmslie, R., Dow, S., 2009, Changes in regulatory T cells in dogs with cancer and associations with tumor type. *J Vet Intern Med* 23, 875-881.
- Oh, D.S., DeMeester, S.R., Vallbohmer, D., Mori, R., Kuramochi, H., Hagen, J.A., Lipham, J., Danenberg, K.D., Danenberg, P.V., Chandrasoma, P., DeMeester, T.R., 2007, Reduction of interleukin 8 gene expression in reflux esophagitis and Barrett's esophagus with antireflux surgery. *Arch Surg* 142, 554-559; discussion 559-560.
- Paoloni, M., Davis, S., Lana, S., Withrow, S., Sangiorgi, L., Picci, P., Hewitt, S., Triche, T., Meltzer, P., Khanna, C., 2009, Canine tumor cross-species genomics uncovers targets linked to osteosarcoma progression. *BMC Genomics* 10, 625.
- Park, S., Cheon, S., Cho, D., 2007, The dual effects of interleukin-18 in tumor progression. *Cell Mol Immunol* 4, 329-335.
- Patruno, R., Arpaia, N., Gadaleta, C.D., Passantino, L., Zizzo, N., Misino, A., Lucarelli, N.M., Catino, A., Valerio, P., Ribatti, D., Ranieri, G., 2009, VEGF

- concentration from plasma-activated platelets rich correlates with microvascular density and grading in canine mast cell tumour spontaneous model. *J Cell Mol Med* 13, 555-561.
- Perry, J.A., Thamm, D.H., Eickhoff, J., Avery, A.C., Dow, S.W., 2010, Increased monocyte chemotactic protein-1 concentration and monocyte count independently associate with a poor prognosis in dogs with lymphoma. *Vet Comp Oncol* 9, 55-64.
- Polanski, M., Anderson, N.L., 2007, A list of candidate cancer biomarkers for targeted proteomics. *Biomark Insights* 1, 1-48.
- Ranen, E., Dank, G., Lavy, E., Perl, S., Lahav, D., Orgad, U., 2007, Oesophageal sarcomas in dogs: Histological and clinical evaluation. *Vet J*.
- Ranen, E., Dank, G., Lavy, E., Perl, S., Lahav, D., Orgad, U., 2008, Oesophageal sarcomas in dogs: histological and clinical evaluation. *Vet J* 178, 78-84.
- Ranen, E., Lavy, E., Aizenberg, I., Perl, S., Harrus, S., 2004, Spirocercosis-associated esophageal sarcomas in dogs. A retrospective study of 17 cases (1997-2003). *Vet Parasitol* 119, 209-221.
- Rebuzzi, L., Willmann, M., Sonneck, K., Gleixner, K.V., Florian, S., Kondo, R., Mayerhofer, M., Vales, A., Gruze, A., Pickl, W.F., Thalhammer, J.G., Valent, P., 2007, Detection of vascular endothelial growth factor (VEGF) and VEGF receptors Flt-1 and KDR in canine mastocytoma cells. *Vet Immunol Immunopathol* 115, 320-333.
- Restucci, B., Borzacchiello, G., Maiolino, P., Martano, M., Paciello, O., Papparella, S., 2004, Expression of Vascular Endothelial Growth Factor Receptor Flk-1 in Canine Mammary Tumours. *Journal of Comparative Pathology* 130, 99-104.
- Restucci, B., Maiolino, P., Paciello, O., Martano, M., De Vico, G., Papparella, S., 2003, Evaluation of Angiogenesis in Canine Seminomas by Quantitative Immunohistochemistry. *Journal of Comparative Pathology* 128, 252-259.
- Restucci, B., Papparella, S., Maiolino, P., De Vico, G., 2002, Expression of vascular endothelial growth factor in canine mammary tumors. *Vet Pathol* 39, 488-493.
- Ribelin, W.E., Bailey, W.S., 1958, Esophageal sarcomas associated with Spirocerca lupi infection in the dog. *Cancer* 11, 1242-1246.
- Ridgway, R.L., Suter, P.F., 1979, Clinical and radiographic signs in primary and metastatic esophageal neoplasms of the dog. *J Am Vet Med Assoc* 174, 700-704.
- Rieder, F., Biancani, P., Harnett, K., Yerian, L., Falk, G.W., 2010, Inflammatory mediators in gastroesophageal reflux disease: impact on esophageal motility, fibrosis, and carcinogenesis. *Am J Physiol Gastrointest Liver Physiol* 298, G571-581.
- Rissetto, K.C., Rindt, H., Selting, K.A., Villamil, J.A., Henry, C.J., Reinero, C.R., 2010, Cloning and expression of canine CD25 for validation of an anti-human CD25 antibody to compare T regulatory lymphocytes in healthy dogs and dogs with osteosarcoma. *Vet Immunol Immunopathol* 135, 137-145.
- Rossmeisl, J.H., Duncan, R.B., Huckle, W.R., Troy, G.C., 2007, Expression of vascular endothelial growth factor in tumors and plasma from dogs with primary intracranial neoplasms. *Am J Vet Res* 68, 1239-1245.

- Rouse, B.T., 2007, Regulatory T cells in health and disease. *J Intern Med* 262, 78-95.
- Sasaki, Y., Yoshimoto, T., Maruyama, H., Tegoshi, T., Ohta, N., Arizono, N., Nakanishi, K., 2005, IL-18 with IL-2 protects against *Strongyloides venezuelensis* infection by activating mucosal mast cell-dependent type 2 innate immunity. *J Exp Med* 202, 607-616.
- Schottenfeld, D., Beebe-Dimmer, J., 2006, Chronic inflammation: a common and important factor in the pathogenesis of neoplasia. *CA Cancer J Clin* 56, 69-83.
- Seibold, H.R., Bailey, W.S., Hoerlein, B.F., Jordan, E.M., Schwabe, C.W., 1955, Observations on the possible relation of malignant esophageal tumors and *Spirocerca lupi* lesions in the dog. *Am J Vet Res* 16, 5-14.
- Shah, S., Divekar, A.A., Hilchey, S.P., Cho, H.M., Newman, C.L., Shin, S.U., Nechustan, H., Challita-Eid, P.M., Segal, B.M., Yi, K.H., Rosenblatt, J.D., 2005, Increased rejection of primary tumors in mice lacking B cells: inhibition of anti-tumor CTL and TH1 cytokine responses by B cells. *Int J Cancer* 117, 574-586.
- Srivastava, S., Salim, N., Robertson, M.J., 2010, Interleukin-18: biology and role in the immunotherapy of cancer. *Curr Med Chem* 17, 3353-3357.
- Stephens, L.C., Gleiser, C.A., Jardine, J.H., 1983, Primary pulmonary fibrosarcoma associated with *Spirocerca lupi* infection in a dog with hypertrophic pulmonary osteoarthropathy. *J Am Vet Med Assoc* 182, 496-498.
- Straubinger, R.K., Greiter, A., McDonough, S.P., Gerold, A., Scanziani, E., Soldati, S., Dailidiene, D., Dailide, G., Berg, D.E., Simpson, K.W., 2003, Quantitative evaluation of inflammatory and immune responses in the early stages of chronic *Helicobacter pylori* infection. *Infect Immun* 71, 2693-2703.
- Tainsky, M.A., 2009, Genomic and proteomic biomarkers for cancer: a multitude of opportunities. *Biochim Biophys Acta* 1796, 176-193.
- Tan, T.T., Coussens, L.M., 2007, Humoral immunity, inflammation and cancer. *Curr Opin Immunol* 19, 209-216.
- Thuwajit, C., Thuwajit, P., Kaewkes, S., Sripa, B., Uchida, K., Miwa, M., Wongkham, S., 2004, Increased cell proliferation of mouse fibroblast NIH-3T3 in vitro induced by excretory/secretory product(s) from *Opisthorchis viverrini*. *Parasitology* 129, 455-464.
- Thuwajit, C., Thuwajit, P., Uchida, K., Daorueang, D., Kaewkes, S., Wongkham, S., Miwa, M., 2006, Gene expression profiling defined pathways correlated with fibroblast cell proliferation induced by *Opisthorchis viverrini* excretory/secretory product. *World J Gastroenterol* 12, 3585-3592.
- Tominaga, M., Horiuchi, Y., Ichikawa, M., Yamashita, M., Okano, K., Jikumaru, Y., Nariai, Y., Kadosawa, T., 2010, Flow cytometric analysis of peripheral blood and tumor-infiltrating regulatory T cells in dogs with oral malignant melanoma. *J Vet Diagn Invest* 22, 438-441.
- Tominaga, M., Horiuchi, Y., Ichikawa, M., Yamashita, M., Okano, K., Jikumaru, Y., Nariai, Y., Kadosawa, T., 2010, Flow cytometric analysis of peripheral blood and tumor-infiltrating regulatory T cells in dogs with oral malignant melanoma. *J Vet Diagn Invest* 22, 438-441.

- Torina, A., Caracappa, S., Barera, A., Dieli, F., Sireci, G., Genchi, C., Deplazes, P., Salerno, A., 2005, Toxocara canis infection induces antigen-specific IL-10 and IFNgamma production in pregnant dogs and their puppies. *Vet Immunol Immunopathol* 108, 247-251.
- Unit, E., Rushbrook, S.M., Marshall, A., Davies, S., Gibbs, P., Morris, L.S., Coleman, N., Alexander, G.J., 2005, Compromised lymphocytes infiltrate hepatocellular carcinoma: the role of T-regulatory cells. *Hepatology* 41, 722-730.
- van der Merwe, L.L., Kirberger, R.M., Clift, S., Williams, M., Keller, N., Naidoo, V., 2008, Spirocerca lupi infection in the dog: a review. *Vet J* 176, 294-309.
- Vanherberghe, M., Day, M.J., Delvaux, F., Gabriel, A., Clercx, C., Peeters, D., 2009, An immunohistochemical study of the inflammatory infiltrate associated with nasal carcinoma in dogs and cats. *J Comp Pathol* 141, 17-26.
- Vennerveld, B.J., Polman, K., 2009, Helminths and malignancy. *Parasite Immunol* 31, 686-696.
- Waugh, D.J., Wilson, C., 2008, The interleukin-8 pathway in cancer. *Clin Cancer Res* 14, 6735-6741.
- Weidner, N., 1995, Intratumor microvessel density as a prognostic factor in cancer. *Am J Pathol* 147, 9-19.
- Wiinberg, B., Spohr, A., Dietz, H.H., Egelund, T., Greiter-Wilke, A., McDonough, S.P., Olsen, J., Priestnall, S., Chang, Y.F., Simpson, K.W., 2005, Quantitative analysis of inflammatory and immune responses in dogs with gastritis and their relationship to Helicobacter spp. infection. *J Vet Intern Med* 19, 4-14.
- Willmann, M., Mullauer, L., Guija de Arespacochaga, A., Reifinger, M., Mosberger, I., Thalhammer, J.G., 2009, Pax5 immunostaining in paraffin-embedded sections of canine non-Hodgkin lymphoma: a novel canine pan pre-B- and B-cell marker. *Vet Immunol Immunopathol* 128, 359-365.
- Wilson, K.T., Crabtree, J.E., 2007, Immunology of Helicobacter pylori: insights into the failure of the immune response and perspectives on vaccine studies. *Gastroenterology* 133, 288-308.
- Wilson, M.S., Maizels, R.M., 2004, Regulation of allergy and autoimmunity in helminth infection. *Clin Rev Allergy Immunol* 26, 35-50.
- Wolf, A.M., Wolf, D., Steurer, M., Gastl, G., Gunsilius, E., Grubeck-Loebenstein, B., 2003, Increase of regulatory T cells in the peripheral blood of cancer patients. *Clin Cancer Res* 9, 606-612.
- Wolfesberger, B., Guija de Arespacohaga, A., Willmann, M., Gerner, W., Miller, I., Schwendenwein, I., Kleiter, M., Egerbacher, M., Thalhammer, J.G., Muellauer, L., Skalicky, M., Walter, I., 2007, Expression of vascular endothelial growth factor and its receptors in canine lymphoma. *J Comp Pathol* 137, 30-40.
- Wolfesberger, B., Tonar, Z., Witter, K., Guija de Arespacohaga, A., Skalicky, M., Walter, I., Thalhammer, J.G., Egger, G.F., 2008, Microvessel density in normal lymph nodes and lymphomas of dogs and their correlation with vascular endothelial growth factor expression. *Res Vet Sci* 85, 56-61.

- Woo, E.Y., Chu, C.S., Goletz, T.J., Schlienger, K., Yeh, H., Coukos, G., Rubin, S.C., Kaiser, L.R., June, C.H., 2001, Regulatory CD4(+)CD25(+) T cells in tumors from patients with early-stage non-small cell lung cancer and late-stage ovarian cancer. *Cancer Res* 61, 4766-4772.
- Xue, L., Lu, H.Q., He, J., Zhao, X.W., Zhong, L., Zhang, Z.Z., Xu, Z.F., 2009, Expression of FOXP3 in esophageal squamous cell carcinoma relating to the clinical data. *Dis Esophagus* 23, 340-346.
- Yonemaru, K., Sakai, H., Murakami, M., Yanai, T., Masegi, T., 2006, Expression of vascular endothelial growth factor, basic fibroblast growth factor, and their receptors (flt-1, flk-1, and flg-1) in canine vascular tumors. *Vet Pathol* 43, 971-980.
- Yoshida, A., Maruyama, H., Kumagai, T., Amano, T., Kobayashi, F., Wang, J., Kuribayashi, K., Ohta, N., 2002, Enhanced UVfemale1 tumor growth in CBF1 mice infected with *Schistosoma mansoni* due to modulation of Th1-like responses. *Parasitol Int* 51, 177-186.

11 APPENDICES

11.1 List of journal publications of work directly related to this thesis

1. Dvir E, Kjelgaard-Hansen M, Mellanby RJ, Schoeman JP. Plasma IL-8 concentrations are increased in dogs with spirocercosis. Accepted to Vet Parasitol.
2. Dvir E, Schoeman JP, Clift SJ, McNeilly TN, Mellanby RJ. Immunohistochemical characterization of lymphocyte and myeloid cell infiltrates in spirocercosis-induced esophageal nodules. Parasite Immunol. 2011. 33:545-553.
3. Dvir E, Clift SJ, Evaluation of selected growth factor expression in canine spirocercosis (*Spirocerca lupi*)-associated non-neoplastic nodules and sarcomas Vet. Parasitol 2010. 174:257–266.
4. Dvir E, Clift SJ, Williams MC. Proposed histological progression of the Spirocerca lupi-induced oesophageal lesion in dogs. Vet Parasitol 2010. 168:71-77.
5. Dvir E, Kirberger RM, Mukorera V, van der Merwe LL, Clift SJ. Clinical differentiation between dogs with benign and malignant spirocercosis. Vet Parasitol 2008. 155: 80-88.

11.2 List of journal publications of work in the same study, but not directly related to this thesis

1. Kirberger RM, Dvir E, van der Merwe L. Canine pneumo-esophagography and the appearance of caudal esophageal masses secondary to Spirocercosis. *J of the Am Vet Med Assoc.* 2012. 240:420-426.
2. Mukorera V, Dvir E, van der Merwe LL, Goddard, A. Serum c-reactive protein concentration in benign and malignant canine spirocercosis. *J. Vet. Int. Med.* 2011. 25:963-966.
3. Mukorera V, van der Merwe LL, Lavy E, Aroch I, Dvir E. Serum alkaline phosphatase activity is not a marker for neoplastic transformation of esophageal nodules in canine spirocercosis. *Vet. Clin. Path.* 2011. 40:389-392.
4. Dvir E, Kirberger RM, Clift SJ, van der Merwe LL. Review: challenges in diagnosis and treatment of canine spirocercosis. *Israel J of Vet Med* 2010. 1:5-10.
5. Kirberger RM, Dvir E, van der Merwe LL. The effect of positioning on the radiographic appearance of caudodorsal mediastinal masses in the dog. *Vet Radiol Ultrasound* 2009. 50:630-634.
6. Dvir E, Perl S, Loeb E, Shklar-Hirsch S, Chai O, Mazaki-Tovi M, Aroch I, Shamir MH. Spinal intramedullary aberrant Spirocerca lupi migration in 3 dogs. *J Vet Intern Med* 2007. 21:860-864.
7. Dvir E, Kirberger RM, Malleczek D. Radiographic and computed tomographic changes and clinical presentation of spirocercosis in the dog. *Vet Radiol & Ultrasound* 2001. 42:119-129.

11.3 List of conference presentations directly related to this thesis

11.3.1 Keynote addresses

1. Dvir, E. Pathological changes with nodule progression. 30th World Veterinary Congress, October 2011, Cape Town, South Africa
2. Dvir, E. Neoplastic transformation in spirocercosis - new research. The 30th World Veterinary Congress, October 2011, Cape Town, South Africa
3. Mukorera, V, **Dvir E.** Benign vs malignant spirocercosis. The 30th World Veterinary Congress, October 2011, Cape Town, South Africa
4. Dvir E. Update on spirocercosis-induced oesophageal sarcoma and *spirocerca lupi* aberrant migration. The 5th South African Veterinary Association (SAVA) Congress, August 2010, Drakensberg, South Africa.
5. Dvir E, Clift SJ. Update on spirocercosis-induced oesophageal sarcoma and *spirocerca lupi* aberrant migration. The 19th Congress of the European College of Veterinary Internal Medicine Companion Animals (ECVIM-CA), September 2009, Porto, Portugal.
6. Dvir E, Kirberger RM, Clift SJ. Spirocercosis-induced oesophageal sarcoma and its clinical complications. The 4th South African Veterinary Association (SAVA) Congress, July 2008, Sun City, South Africa.
7. Williams MC, Clift SJ, **Dvir E.** The oesophageal nodule in canine spirocercosis – a fascinating phenomenon. The 4th South African Veterinary Association (SAVA) Congress, July 2008, Sun City, South Africa

11.3.2 Research abstracts

1. Dvir E, Mellanby RJ, van der Merwe LL, Kjelgaard-Hansen M, Schoeman JP. Differences in the plasma cytokine milieu between dogs with benign and malignant spirocercosis. The 21th Congress of the European College of Veterinary Internal Medicine Companion Animals (ECVIM-CA), September 2011, Seville, Spain.
2. Dvir E, Schoeman JP, McNeilly TN, Clift SJ, Mellanby RJ. Characterisation of regulatory t cell, t and b lymphocyte and myeloid cell infiltrates in spirocercosis-induced oesophageal nodules. The 20th Congress of the European College of Veterinary Internal Medicine Companion Animals (ECVIM-CA), September 2010, Toulouse, France.
3. Dvir E, Clift SJ. Selected growth factor expression in *Spirocerca lupi* esophageal nodules. Congress of the American College of Veterinary Internal Medicine (ACVIM), June 2010, Anaheim, California.
4. Dvir E, Clift SJ. The spirocercosis-induced oesophageal nodule: progression from inflammation to sarcoma. The 19th Congress of the European College of Veterinary Internal Medicine Companion Animals (ECVIM-CA), September 2009, Porto, Portugal.
5. Dvir E, Kirberger RM, Mokarera V, van der Merwe LL, Clift SJ. Clinicopathological differences between dogs with benign and malignant spirocercosis-induced oesophageal nodules. The 17th Congress of the European College of Veterinary Internal Medicine Companion Animals (ECVIM-CA), September 2007, Budapest, Hungary