REFERENCES

Alexandrie AK, Nyberg F, Warholm M, Rannug A. Influence of CYP1A1, GSTM1, GSTT1, and NQO1 genotypes and cumulative smoking dose on lung cancer risk in a Swedish population. ***Cancer Epidemiol Biomarkers Prev*** 2004; 13: 908-14.

Angulo P, Lindor KD. Primary sclerosing cholangitis. ***Hepatology*** 1999; 30: 325-32.

Anwar A, Dehn D, Siegel D, Kepa JK, Tang LJ, Pietenpol JA, Ross D. Interaction of human NAD(P)H: quinone oxidoreductase 1 (NQO1) with the tumor suppressor protein p53 in cells and cell-free systems. ***J Biol Chem*** 2003; 278: 10368-73.

Asher G, Lotem J, Kama R, Sachs L, Shaul Y. NQO1 stabilizes p53 through a distinct pathway. ***Proc Natl Acad Sci U S A*** 2002; 99: 3099-104.

Asher G, Shaul Y. Ubiquitin-independent degradation: lessons from the p53 model. ***Isr Med Assoc J*** 2006; 8: 229-32.

Bartsch H, Malaveille C, Lowenfels AB, Maisonneuve P, Hautefeuille A, Boyle P. Genetic polymorphism of N-acetyltransferases, glutathione S-transferase M1 and NAD(P)H:quinone oxidoreductase in relation to malignant and benign pancreatic disease risk. The International Pancreatic Disease Study Group. ***Eur J Cancer Prev*** 1998; 7: 215-23.

Begleiter A, Hewitt D, Gibson SB, Johnston JB. Investigation of an NQO1 polymorphism as a possible risk and prognostic factor for chronic lymphocytic leukemia. ***Leuk Res*** 2008.

Bian JT, Zhao HL, Zhang ZX, Bi XH, Zhang JW. Association of NAD(P)H:quinone oxidoreductase 1 polymorphism and Alzheimer's disease in Chinese. ***J Mol Neurosci*** 2008; 34: 235-40.

Broberg K, Bjork J, Paulsson K, Hoglund M, Albin M. Constitutional short telomeres are strong genetic susceptibility markers for bladder cancer. ***Carcinogenesis*** 2005; 26: 1263-71.

Cadenas E, Hochstein P, Ernster L. Pro- and antioxidant functions of quinones and quinone reductases in mammalian cells. ***Adv Enzymol Relat Areas Mol Biol*** 1992; 65: 97-146.

Chao C, Zhang ZF, Berthiller J, Boffetta P, Hashibe M. NAD(P)H: quinone oxidoreductase 1 (NQO1) Pro 187 Ser polymorphism and the risk of lung, bladder, and colorectal cancers: a meta-analysis. ***Cancer Epidemiol Biomarkers Prev*** 2006; 15: 979-87.

Chen H, Lum A, Seifried A, Wilkens LR, Le Marchand L. Association of the NAD(P)H:quinone oxidoreductase 609C-->T polymorphism with a decreased lung cancer risk. ***Cancer Res*** 1999; 59: 3045-8.

Chen LZ, Harris PC, Apostolou S, Baker E, Holman K, Lane SA, Nancarrow JK, Whitmore SA, Stallings RL, Hildebrand CE, et al. A refined physical map of the long arm of human chromosome 16. ***Genomics*** 1991; 10: 308-12.

Chesis PL, Levin DE, Smith MT, Ernster L, Ames BN. Mutagenicity of quinones: pathways of metabolic activation and detoxification. ***Proc Natl Acad Sci U S A*** 1984; 81: 1696-700.

Choi JY, Lee KM, Cho SH, Kim SW, Choi HY, Lee SY, Im HJ, Yoon KJ, Choi H, Choi I, Hirvonen A, Hayes RB, Kang D. CYP2E1 and NQO1 genotypes, smoking and bladder cancer. ***Pharmacogenetics*** 2003; 13: 349-55.

Cullen JJ, Hinkhouse MM, Grady M, Gaut AW, Liu J, Zhang YP, Weydert CJ, Domann FE, Oberley LW. Dicumarol inhibition of NADPH: quinone oxidoreductase induces growth inhibition of pancreatic cancer via a superoxide-mediated mechanism. ***Cancer Res*** 2003; 63: 5513-20.

de Groen PC, Gores GJ, LaRusso NF, Gunderson LL, Nagorney DM. Biliary tract cancers. ***N Engl J Med*** 1999; 341: 1368-78.

di Martino E, Hardie LJ, Wild CP, Gong YY, Olliver JR, Gough MD, Bird NC. The NAD(P)H:quinone oxidoreductase I C609T polymorphism modifies the risk of Barrett esophagus and esophageal adenocarcinoma. ***Genet Med*** 2007; 9: 341-7.

Favreau LV, Pickett CB. Transcriptional regulation of the rat NAD(P)H:quinone reductase gene. Identification of regulatory elements controlling basal level expression and inducible expression by planar aromatic compounds and phenolic antioxidants. ***J Biol Chem*** 1991; 266: 4556-61.

Fleming RA, Drees J, Loggie BW, Russell GB, Geisinger KR, Morris RT, Sachs D, McQuellon RP. Clinical significance of a NAD(P)H: quinone oxidoreductase 1 polymorphism in patients with disseminated peritoneal cancer receiving intraperitoneal hyperthermic chemotherapy with mitomycin C. ***Pharmacogenetics*** 2002; 12: 31-7.

Fong CS, Wu RM, Shieh JC, Chao YT, Fu YP, Kuao CL, Cheng CW. Pesticide exposure on southwestern Taiwanese with MnSOD and NQO1 polymorphisms is associated with increased risk of Parkinson's disease. ***Clin Chim Acta*** 2007; 378: 136-41.

Gaedigk A, Tyndale RF, Jurima-Romet M, Sellers EM, Grant DM, Leeder JS. NAD(P)H:quinone oxidoreductase: polymorphisms and allele frequencies in Caucasian, Chinese and Canadian Native Indian and Inuit populations. ***Pharmacogenetics*** 1998; 8: 305-13.

Ganousis LG, Goon D, Zyglewska T, Wu KK, Ross D. Cell-specific metabolism in mouse bone marrow stroma: studies of activation and detoxification of benzene metabolites. ***Mol Pharmacol*** 1992; 42: 1118-25.

Gelboin HV. Benzo[alpha]pyrene metabolism, activation and carcinogenesis: role and regulation of mixed-function oxidases and related enzymes. ***Physiol Rev*** 1980; 60: 1107-66.

Goldberg MJ. Cholangiocarcinoma. ***Dis Mon*** 2004; 50: 540-4.

Gong X, Kole L, Iskander K, Jaiswal AK. NRH:quinone oxidoreductase 2 and NAD(P)H:quinone oxidoreductase 1 protect tumor suppressor p53 against 20s proteasomal degradation leading to stabilization and activation of p53. ***Cancer Res*** 2007; 67: 5380-8.

Gores GJ. Cholangiocarcinoma: current concepts and insights. ***Hepatology*** 2003; 37: 961-9.

Gustafson DL, Siegel D, Rastatter JC, Merz AL, Parpal JC, Kepa JK, Ross D, Long ME. Kinetics of NAD(P)H:quinone oxidoreductase I (NQO1) inhibition by mitomycin C in vitro and in vivo. ***J Pharmacol Exp Ther*** 2003; 305: 1079-86.

Hamajima N, Matsuo K, Iwata H, Shinoda M, Yamamura Y, Kato T, Hatooka S, Mitsudomi T, Suyama M, Kagami Y, Ogura M, Ando M, Sugimura Y, Tajima K. NAD(P)H: quinone oxidoreductase 1 (NQO1) C609T polymorphism and the risk of eight cancers for Japanese. ***Int J Clin Oncol*** 2002; 7: 103-8.

Holzinger F, Z'Graggen K, Buchler MW. Mechanisms of biliary carcinogenesis: a pathogenetic multi-stage cascade towards cholangiocarcinoma. ***Ann Oncol*** 1999; 10 Suppl 4: 122-6.

Hori H, Ohmori O, Matsumoto C, Shinkai T, Nakamura J. NAD(P)H: quinone oxidoreductase (NQO1) gene polymorphism and schizophrenia. ***Psychiatry Res*** 2003; 118: 235-9.

Hu LT, Stamberg J, Pan S. The NAD(P)H:quinone oxidoreductase locus in human colon carcinoma HCT 116 cells resistant to mitomycin C. ***Cancer Res*** 1996; 56: 5253-9.

Jaiswal AK. Human NAD(P)H:quinone oxidoreductase (NQO1) gene structure and induction by dioxin. ***Biochemistry*** 1991; 30: 10647-53.

Jaiswal AK. Characterization and partial purification of microsomal NAD(P)H: quinone oxidoreductases. ***Arch Biochem Biophys*** 2000; 375: 62-8.

Jemal A, Murray T, Samuels A, Ghafoor A, Ward E, Thun MJ. Cancer statistics, 2003. ***CA Cancer J Clin*** 2003; 53: 5-26.

Joseph P, Long DJ, 2nd, Klein-Szanto AJ, Jaiswal AK. Role of NAD(P)H:quinone oxidoreductase 1 (DT diaphorase) in protection against quinone toxicity. ***Biochem Pharmacol*** 2000; 60: 207-14.

Kelsey KT, Ross D, Traver RD, Christiani DC, Zuo ZF, Spitz MR, Wang M, Xu X, Lee BK, Schwartz BS, Wiencke JK. Ethnic variation in the prevalence of a common NAD(P)H quinone oxidoreductase polymorphism and its implications for anti-cancer chemotherapy. ***Br J Cancer*** 1997; 76: 852-4.

Khan SA, Thomas HC, Davidson BR, Taylor-Robinson SD. Cholangiocarcinoma. ***Lancet*** 2005; 366: 1303-14.

Kiffmeyer WR, Langer E, Davies SM, Envall J, Robison LL, Ross JA. Genetic polymorphisms in the Hmong population: implications for cancer etiology and survival. ***Cancer*** 2004; 100: 411-7.

Krajinovic M, Sinnett H, Richer C, Labuda D, Sinnett D. Role of NQO1, MPO and CYP2E1 genetic polymorphisms in the susceptibility to childhood acute lymphoblastic leukemia. ***Int J Cancer*** 2002; 97: 230-6.

Lan Q, Mumford JL, Shen M, Demarini DM, Bonner MR, He X, Yeager M, Welch R, Chanock S, Tian L, Chapman RS, Zheng T, Keohavong P, Caporaso N, Rothman N. Oxidative damage-related genes AKR1C3 and OGG1 modulate risks for lung cancer due to exposure to PAH-rich coal combustion emissions. ***Carcinogenesis*** 2004; 25: 2177-81.

Landi L, Fiorentini D, Galli MC, Segura-Aguilar J, Beyer RE. DT-Diaphorase maintains the reduced state of ubiquinones in lipid vesicles thereby promoting their antioxidant function. ***Free Radic Biol Med*** 1997; 22: 329-35.

Lazaridis KN, Gores GJ. Cholangiocarcinoma. ***Gastroenterology*** 2005; 128: 1655-67.

Lee MA, Woo IS, Kang JH, Hong YS, Lee KS. Epirubicin, cisplatin, and protracted infusion of 5-FU (ECF) in advanced intrahepatic cholangiocarcinoma. ***J Cancer Res Clin Oncol*** 2004; 130: 346-50.

Lewis SJ, Cherry NM, Niven RM, Barber PV, Povey AC. Polymorphisms in the NAD(P)H: quinone oxidoreductase gene and small cell lung cancer risk in a UK population. ***Lung Cancer*** 2001; 34: 177-83.

Li Y, Cao Z, Zhu H. Upregulation of endogenous antioxidants and phase 2 enzymes by the red wine polyphenol, resveratrol in cultured aortic smooth muscle cells leads to cytoprotection against oxidative and electrophilic stress. ***Pharmacol Res*** 2006; 53: 6-15.

Li Y, Jaiswal AK. Human antioxidant-response-element-mediated regulation of type 1 NAD(P)H: quinone oxidoreductase gene expression. Effect of sulfhydryl modifying agents. ***Eur J Biochem*** 1994; 226: 31-9.

Lim JH. Cholangiocarcinoma: morphologic classification according to growth pattern and imaging findings. ***AJR Am J Roentgenol*** 2003; 181: 819-27.

Lind C, Cadenas E, Hochstein P, Ernster L. DT-diaphorase: purification, properties, and function. ***Methods Enzymol*** 1990; 186: 287-301.

Lind C, Hochstein P, Ernster L. DT-diaphorase as a quinone reductase: a cellular control device against semiquinone and superoxide radical formation. ***Arch Biochem Biophys*** 1982; 216: 178-85.

Liu C, Wang J, Ou QJ. Possible stem cell origin of human cholangiocarcinoma. ***World J Gastroenterol*** 2004; 10: 3374-6.

Long DJ, 2nd, Waikel RL, Wang XJ, Perlaky L, Roop DR, Jaiswal AK. NAD(P)H :quinone oxidoreductase 1 deficiency increases susceptibility to benzo(a) pyrene-induced mouse skin carcinogenesis. ***Cancer Res*** 2000; 60: 5913-5.

Lyn-Cook BD, Yan-Sanders Y, Moore S, Taylor S, Word B, Hammons GJ. Increased levels of NAD(P)H: quinone oxidoreductase 1 (NQO1) in pancreatic tissues from smokers and pancreatic adenocarcinomas: A potential biomarker of early damage in the pancreas. ***Cell Biol Toxicol*** 2006; 22: 73-80.

Maltoni C, Conti B, Cotti G. Benzene: a multipotential carcinogen. Results of long-term bioassays performed at the Bologna Institute of Oncology. ***Am J Ind Med*** 1983; 4: 589-630.

Misra V, Klamut HJ, Rauth AM. Transfection of COS-1 cells with DT-diaphorase cDNA: role of a base change at position 609. ***Br J Cancer*** 1998; 77: 1236-40.

Mitrou PN, Watson MA, Loktionov AS, Cardwell C, Gunter MJ, Atkin WS, Macklin CP, Cecil T, Bishop DT, Primrose J, Bingham SA. Role of NQO1 C609T and EPHX1 gene polymorphisms in the association of smoking and alcohol with sporadic distal colorectal adenomas: results from the UKFSS Study. ***Carcinogenesis*** 2007; 28: 875-82.

Moore LE, Wiencke JK, Bates MN, Zheng S, Rey OA, Smith AH. Investigation of genetic polymorphisms and smoking in a bladder cancer case-control study in Argentina. ***Cancer Lett*** 2004; 211: 199-207.

Morrison H, Di Monte D, Nordenskjold M, Jernstrom B. Induction of cell damage by menadione and benzo(a)pyrene-3,6-quinone in cultures of adult rat hepatocytes and human fibroblasts. ***Toxicol Lett*** 1985; 28: 37-47.

Nakanuma Y, Harada K, Kaji K, Terasaki S, Tsuneyama K, Moteki S, Van de Water J, Leung PS, Gershwin ME. Clinicopathological study of primary biliary cirrhosis negative for antimitochondrial antibodies. ***Liver*** 1997; 17: 281-7.

Nioi P, Hayes JD. Contribution of NAD(P)H:quinone oxidoreductase 1 to protection against carcinogenesis, and regulation of its gene by the Nrf2 basic-region leucine zipper and the arylhydrocarbon receptor basic helix-loop-helix transcription factors. ***Mutat Res*** 2004; 555: 149-71.

Ohshima H, Bandaletova TY, Brouet I, Bartsch H, Kirby G, Ogunbiyi F, Vatanasapt V, Pipitgool V. Increased nitrosamine and nitrate biosynthesis mediated by nitric oxide synthase induced in hamsters infected with liver fluke (Opisthorchis viverrini). ***Carcinogenesis*** 1994; 15: 271-5.

Okuda K, Nakanuma Y, Miyazaki M. Cholangiocarcinoma: recent progress. Part 1: epidemiology and etiology. ***J Gastroenterol Hepatol*** 2002; 17: 1049-55.

Pan SS, Forrest GL, Akman SA, Hu LT. NAD(P)H: quinone oxidoreductase expression and mitomycin C resistance developed by human colon cancer HCT 116 cells. ***Cancer Res*** 1995; 55: 330-5.

Park SJ, Zhao H, Spitz MR, Grossman HB, Wu X. An association between NQO1 genetic polymorphism and risk of bladder cancer. ***Mutat Res*** 2003; 536: 131-7.

Patel T. Cholangiocarcinoma. ***Nat Clin Pract Gastroenterol Hepatol*** 2006; 3: 33-42.

Patt YZ, Hassan MM, Lozano RD, Waugh KA, Hoque AM, Frome AI, Lahoti S, Ellis L, Vauthey JN, Curley SA, Schnirer, II, Raijman I. Phase II trial of cisplatin, interferon alpha-2b, doxorubicin, and 5-fluorouracil for biliary tract cancer. ***Clin Cancer Res*** 2001; 7: 3375-80.

Pinkus R, Weiner LM, Daniel V. Role of oxidants and antioxidants in the induction of AP-1, NF-kappaB, and glutathione S-transferase gene expression. ***J Biol Chem*** 1996; 271: 13422-9.

Pinlaor S, Hiraku Y, Ma N, Yongvanit P, Semba R, Oikawa S, Murata M, Sripa B, Sithithaworn P, Kawanishi S. Mechanism of NO-mediated oxidative and nitrative DNA damage in hamsters infected with Opisthorchis viverrini: a model of inflammation-mediated carcinogenesis. ***Nitric Oxide*** 2004; 11: 175-83.

Prawan A, Kukongviriyapan V, Tassaneeyakul W, Pairojkul C, Bhudhisawasdi V. Association between genetic polymorphisms of CYP1A2, arylamine N-acetyltransferase 1 and 2 and susceptibility to cholangiocarcinoma. ***Eur J Cancer Prev*** 2005; 14: 245-50.

Prestera T, Holtzclaw WD, Zhang Y, Talalay P. Chemical and molecular regulation of enzymes that detoxify carcinogens. ***Proc Natl Acad Sci U S A*** 1993; 90: 2965-9.

Roskams T. Liver stem cells and their implication in hepatocellular and cholangiocarcinoma. ***Oncogene*** 2006; 25: 3818-22.

Ross D. Functions and distribution of NQO1 in human bone marrow: potential clues to benzene toxicity. ***Chem Biol Interact*** 2005; 153-154: 137-46.

Ross D, Kepa JK, Winski SL, Beall HD, Anwar A, Siegel D. NAD(P)H:quinone oxidoreductase 1 (NQO1): chemoprotection, bioactivation, gene regulation and genetic polymorphisms. ***Chem Biol Interact*** 2000; 129: 77-97.

Saldivar SJ, Wang Y, Zhao H, Shao L, Lin J, Spitz MR, Wu X. An association between a NQO1 genetic polymorphism and risk of lung cancer. ***Mutat Res*** 2005; 582: 71-8.

Seedhouse C, Bainton R, Lewis M, Harding A, Russell N, Das-Gupta E. The genotype distribution of the XRCC1 gene indicates a role for base excision repair in the development of therapy-related acute myeloblastic leukemia. ***Blood*** 2002; 100: 3761-6.

Shaib YH, El-Serag HB, Davila JA, Morgan R, McGlynn KA. Risk factors of intrahepatic cholangiocarcinoma in the United States: a case-control study. ***Gastroenterology*** 2005; 128: 620-6.

Shaw PM, Reiss A, Adesnik M, Nebert DW, Schembri J, Jaiswal AK. The human dioxin-inducible NAD(P)H: quinone oxidoreductase cDNA-encoded protein expressed in COS-1 cells is identical to diaphorase 4. ***Eur J Biochem*** 1991; 195: 171-6.

Siegel D, Bolton EM, Burr JA, Liebler DC, Ross D. The reduction of alpha-tocopherolquinone by human NAD(P)H: quinone oxidoreductase: the role of alpha-tocopherolhydroquinone as a cellular antioxidant. ***Mol Pharmacol*** 1997; 52: 300-5.

Siegel D, Ross D. Immunodetection of NAD(P)H:quinone oxidoreductase 1 (NQO1) in human tissues. ***Free Radic Biol Med*** 2000; 29: 246-53.

Sirica AE. Cholangiocarcinoma: molecular targeting strategies for chemoprevention and therapy. ***Hepatology*** 2005; 41: 5-15.

Skibo EB, Gordon S, Bess L, Boruah R, Heileman MJ. Studies of pyrrolo[1,2-alpha]benzimidazolequinone DT-diaphorase substrate activity, topoisomerase II inhibition activity, and DNA reductive alkylation. ***J Med Chem*** 1997; 40: 1327-39.

Skuladottir H, Autrup H, Autrup J, Tjoenneland A, Overvad K, Ryberg D, Haugen A, Olsen JH. Polymorphisms in genes involved in xenobiotic metabolism and lung cancer risk under the age of 60 years. A pooled study of lung cancer patients in Denmark and Norway. ***Lung Cancer*** 2005; 48: 187-99.

Smith MT, Wang Y, Skibola CF, Slater DJ, Lo Nigro L, Nowell PC, Lange BJ, Felix CA. Low NAD(P)H:quinone oxidoreductase activity is associated with increased risk of leukemia with MLL translocations in infants and children. ***Blood*** 2002; 100: 4590-3.

Sripa B, Kaewkes S, Sithithaworn P, Mairiang E, Laha T, Smout M, Pairojkul C, Bhudhisawasdi V, Tesana S, Thinkamrop B, Bethony JM, Loukas A, Brindley PJ. Liver fluke induces cholangiocarcinoma. ***PLoS Med*** 2007; 4: e201.

Sriplung H, Wiangnon S, Sontipong S, Sumitsawan Y, Martin N. Cancer incidence trends in Thailand, 1989-2000. ***Asian Pac J Cancer Prev*** 2006; 7: 239-44.

Stanulla M, Dynybil C, Bartels DB, Dordelmann M, Loning L, Claviez A, Schrappe M. The NQO1 C609T polymorphism is associated with risk of secondary malignant neoplasms after treatment for childhood acute lymphoblastic leukemia: a matched-pair analysis from the ALL-BFM study group. ***Haematologica*** 2007; 92: 1581-2.

Steiner M, Hillenbrand M, Borkowsi M, Seiter H, Schuff-Werner P. 609 C --> T polymorphism in NAD(P)H:quinone oxidoreductase gene in patients with prostatic adenocarcinoma or benign prostatic hyperplasia. ***Cancer Lett*** 1999; 135: 67-71.

Strassburg A, Strassburg CP, Manns MP, Tukey RH. Differential gene expression of NAD(P)H:quinone oxidoreductase and NRH:quinone oxidoreductase in human hepatocellular and biliary tissue. ***Mol Pharmacol*** 2002; 61: 320-5.

Sun Y. p53 and its downstream proteins as molecular targets of cancer. ***Mol Carcinog*** 2006; 45: 409-15.

Terry PD, Umbach DM, Taylor JA. No association between SOD2 or NQO1 genotypes and risk of bladder cancer. ***Cancer Epidemiol Biomarkers Prev*** 2005; 14: 753-4.

Thor H, Smith MT, Hartzell P, Bellomo G, Jewell SA, Orrenius S. The metabolism of menadione (2-methyl-1,4-naphthoquinone) by isolated hepatocytes. A study of the implications of oxidative stress in intact cells. ***J Biol Chem*** 1982; 257: 12419-25.

Tullo A, D'Erchia AM, Honda K, Kelly MD, Habib NA, Saccone C, Sbisa E. New p53 mutations in hilar cholangiocarcinoma. ***Eur J Clin Invest*** 2000; 30: 798-803.

Upatham ES, Viyanant V. Opisthorchis viverrini and opisthorchiasis: a historical review and future perspective. ***Acta Trop*** 2003; 88: 171-6.

Uttaravichien T, Bhudhisawasdi V, Pairojkul C, Pugkhem A. The intrahepatic cholangiocarcinoma in Thailand. ***J Hepatobiliary Pancreat Surg*** 1999; 6: 128-35.

van der Logt EM, Bergevoet SM, Roelofs HM, Te Morsche RH, Dijk Y, Wobbes T, Nagengast FM, Peters WH. Role of epoxide hydrolase, NAD(P)H:quinone oxidoreductase, cytochrome P450 2E1 or alcohol dehydrogenase genotypes in susceptibility to colorectal cancer. ***Mutat Res*** 2006; 593: 39-49.

Vatanasapt V, Sriamporn S, Vatanasapt P. Cancer control in Thailand. ***Jpn J Clin Oncol*** 2002; 32 Suppl: S82-91.

Vatanasapt V, Uttaravichien T, Mairiang EO, Pairojkul C, Chartbanchachai W, Haswell-Elkins M. Cholangiocarcinoma in north-east Thailand. ***Lancet*** 1990; 335: 116-7.

Venugopal R, Jaiswal AK. Nrf2 and Nrf1 in association with Jun proteins regulate antioxidant response element-mediated expression and coordinated induction of genes encoding detoxifying enzymes. ***Oncogene*** 1998; 17: 3145-56.

Wiemels J, Wiencke JK, Varykoni A, Smith MT. Modulation of the toxicity and macromolecular binding of benzene metabolites by NAD(P)H:Quinone oxidoreductase in transfected HL-60 cells. ***Chem Res Toxicol*** 1999; 12: 467-75.

Wiencke JK, Spitz MR, McMillan A, Kelsey KT. Lung cancer in Mexican-Americans and African-Americans is associated with the wild-type genotype of the NAD(P)H: quinone oxidoreductase polymorphism. ***Cancer Epidemiol Biomarkers Prev*** 1997; 6: 87-92.

Workman P. Enzyme-directed bioreductive drug development revisited: a commentary on recent progress and future prospects with emphasis on quinone anticancer agents and quinone metabolizing enzymes, particularly DT-diaphorase. ***Oncol Res*** 1994; 6: 461-75.

Wu T (2005). Cyclooxygenase-2 and prostaglandin signaling in cholangiocarcinoma. *In* "Biochim Biophys Acta", Vol. 1755, pp. 135-50.

Yamagiwa H, Tomiyama H. Intestinal metaplasia-dysplasia-carcinoma sequence of the gallbladder. ***Acta Pathol Jpn*** 1986; 36: 989-97.

Zhang J, Schulz WA, Li Y, Wang R, Zotz R, Wen D, Siegel D, Ross D, Gabbert HE, Sarbia M. Association of NAD(P)H: quinone oxidoreductase 1 (NQO1) C609T polymorphism with esophageal squamous cell carcinoma in a German Caucasian and a northern Chinese population. ***Carcinogenesis*** 2003; 24: 905-9.

APPENDICES

APPENDIX A
REAGENTS

1. Reagents for cell membrane lysis buffer

0.32 M Sucrose

5% V/V Triton X-100

5 mM MgCl2-6H2O

12 mM Tris-HCl, pH 7.6

Prepare cell membrane lysis buffer in distilled water, autoclave and store at 4°C.

2. Reagents for nuclear membrane lysis buffer

4 M Guanidine HCL

12 mM Tris-HCl, pH 7.6

375 mM NaCl

12 M EDTA, pH 8.0

0.5% Sodium N-Lauroyl Sarcosinate

0.1 M β-Mercaptoethanol

Prepare nuclear membrane lysis buffer in distilled water, autoclave and store at 4°C.

3. Reagents for 10X TBE buffer

0.9 M Tris-Base

0.9 M Boric acid

5 M EDTA, pH 8.0

Prepare 10X TBE buffer in distilled water, autoclave and store at 4°C.

4. Reagents for 6x loading dye buffer

40% Sucrose

0.25% Bromophenol blue

Prepare loading dye buffer in distilled water and store at -20°C.

มหาวิทยาลัยขอนแก่น

หนังสือฉบับนี้ให้ไว้เพื่อแสดงว่า

โครงการวิจัยเรื่อง : ความผิดแผกทางพันธุกรรมของ NAD(P)H-quinone oxidoreductase-1 (NQO1) และ glutathione S-transferases (GSTM1, GSTT1 และ GSTP1) กับความเสี่ยงต่อมะเร็งท่อน้ำดีในประชากรไทย ภาคตะวันออกเฉียงเหนือ

(Polymorphisms of NAD(P)H-quinone oxidoreductase-1 (NQO1) and glutathione S-transferases (GSTM1, GSTT1 and GSTP1) and susceptibility to cholangiocarcinoma in Northeastern Thais)

หัวหน้าโครงการวิจัย : อาจารย์เอื้อมเดือน ประวาฬ และคณะ

หน่วยงานที่สังกัด : ภาควิชาเภสัชวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น

เอกสารที่รับรอง : 1. เบบเสนอเพื่อขอรับการพิจารณาจริยธรรมการวิจัยในมนุษย์ version 1.0 ฉบับลงวันที่ 18 กุมภาพันธ์ 2552

2. โครงร่างการวิจัย version 1.0 ฉบับลงวันที่ 18 กุมภาพันธ์ 2552

3. เบบบันทึกข้อมูลการวิจัย version 1.0 ฉบับลงวันที่ 18 กุมภาพันธ์ 2552

ได้ผ่านการรับรองจากคณะกรรมการจริยธรรมการวิจัยในมนุษย์มหาวิทยาลัยขอนแก่น โดยยึดหลักเกณฑ์ตามคำประกาศเฮลซิงกิ (Declaration of Helsinki) และแนวทางการปฏิบัติการวิจัยทางคลินิกที่ดี (ICH GCP)

ให้ไว้ ณ วันที่ 3 มีนาคม พ.ศ. 2552

(รองศาสตราจารย์จิราภรณ์ ศรีนิครินทร์)

ประธานคณะกรรมการจริยธรรมการวิจัยในมนุษย์

ประจำสาขาวิชาทางชีวเวชศาสตร์และการวิจัยทางการแพทย์

มหาวิทยาลัยขอนแก่น

ลำดับที่ 3.4.01 : 05/2552

เลขที่: HE521047 วันหมดอายุ 2 มีนาคม พ.ศ. 2553

คณะกรรมการจริยธรรมการวิจัยในมนุษย์มหาวิทยาลัยขอนแก่น (Institutional Review Board Number; IRB00001189
ห้อง 1733 ชั้น 13 อาคารสมเด็จพระศรีนครินทราบรมราชนนี อนุสรณ์ Federal Wide Assurance; FWA00003418
คณะแพทยศาสตร์ โทร. (043) 366616-17

APPENDIX B
LIST OF COMMUNICATIONS

Communications:

1. POSTER PRESENTATION:

1.1 "Genetic polymorphism of NAD(P)H-quinone oxidoreductase-1 in Thais and its association with cholangiocarcinoma" in ***The 3rd Asian Pacific Regional ISSX Meeting.*** The imperial queen's park Hotel, Bangkok; 10-12 May 2009.

1.2 "NAD(P)H-quinone oxidoreductase-1 (NQO1) C609T genotypes in the Thai population" in ***The 31st Pharmacological and Therapeutic Society of Thailand Meeting.*** Khon Kaen University; 18-20 March 2009. (*Best presentation Award*)

2. PROCEEDING:

2.1 Zeekpudsa P, Prawan A, Kukongviriyaoan V and Bhudhisawasdi V. NAD(P)H-quinone oxidoreductase-1 (NQO1) C609T genotypes in the Thai population. ***Thai J Pharmacol.*** *2009; 31(1): 57-60.*

ISSX | International Society for the Study of Xenobiotics

3rd Asian Pacific Regional Meeting

Understanding Xenobiotics for Better Drug Development and Therapy

The Imperial Queen's Park Hotel | Bangkok, Thailand | 10 - 12 May 2009

Abstracts

125. POLYMORPHISMS IN THE PROMOTER REGION OF UGT1A9 GENE IN THAIS

Pomtipa Korpresertthawom[1], Krongtong Yoovathawom[2] and Wandee Udomuksorn[3]
[1]Department of Pharmacology, Faculty of Science, Mahidol University, Bangkok, Thailand, 10400, [2]Department of Pharmacology and Multidisciplinary Unit, Faculty of Science, Mahidol University, Bangkok, Thailand, 10400, [3]Department of Pharmacology, Faculty of Science, Prince of Songkla University, Songkhla, Thailand, 90112

The human UDP-glucuronosyltransferase, UGT1A9, catalyzes glucuronidation of various endobiotics and xenobiotics. Genetic polymorphisms of *UGT1A9* can influence detoxifying capacities and have considerable effect on the metabolisms of numerous drugs. The purpose of this study was to investigate the polymorphisms in the 5□-flanking region of *UGT1A9* gene in Thai population. Genomic DNA from 93 healthy unrelated volunteers was amplified by the polymerase chain reaction (PCR) and DNA sequencing was performed to determine mutations. There was a novel single nucleotide polymorphism (SNP) in *UGT1A9* promoter region, heterozygous -688A>C, with frequency of 0.2473. In addition, three known polymorphisms were found, -440T>C, -331C>T and one base insertion of thymidine resulting in -118A(T)$_{10}$AT (*UGT1A9*1b*), with frequencies of 0.9785, 0.9677 and 0.5323, respectively. In conclusion, this is the first study to demonstrate the genetic variations in the promoter region of *UGT1A9* gene in Thai population.

126. GENETIC POLYMORPHISM OF NAD(P)H-QUINONE OXIDOREDUCTASE-1 IN THAIS AND ITS ASSOCIATION WITH CHOLANGIOCARCINOMA

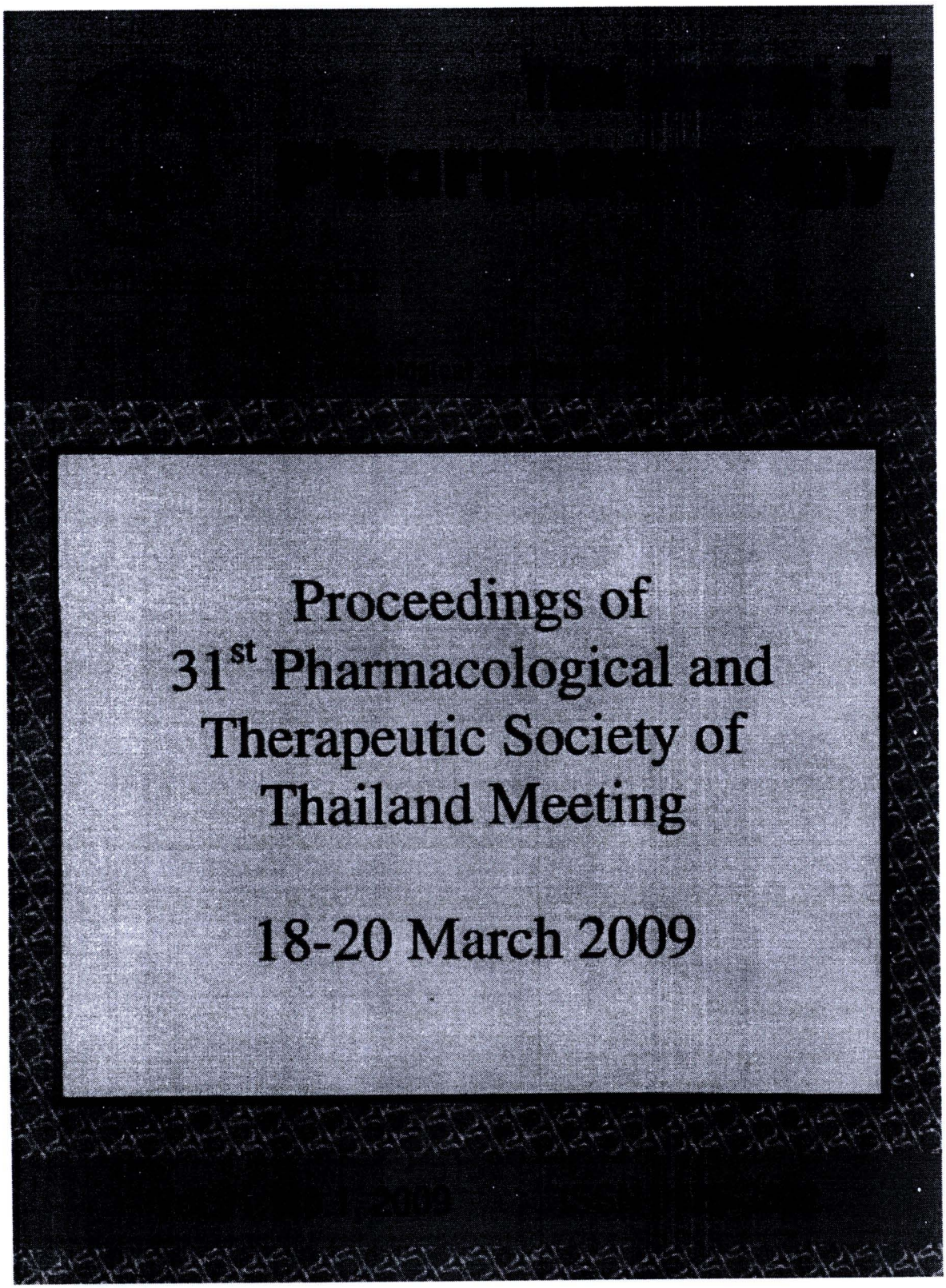
Pornsin Zeekpudsa, Auemduan Prawan, Veerapol Kukongviriyapan and Vajarabhongsa Bhudhisawasdi
Department of Pharmacology, Faculty of Medicine, Liver Fluke and Cholangiocarcinoma Research Center, Khon Kaen University, Khon Kaen, Thailand, 40002

NAD(P)H-quinone oxidoreductase-1 (NQO1) is a detoxifying/antioxidant enzyme that plays a critical role in cellular defense against reactive oxygen species and toxic quinone derivatives, which in turn confer cytoprotection, inhibition of mutation and carcinogenesis. The gene coding for NQO1 has a genetic polymorphism (C→T) at nucleotide position 609 (amino acid codon 187) of the NQO1 cDNA. This mutation has been associated with a decreased enzymatic activity, and increased risk of chemically-induced cytoxicity and susceptibility to various forms of cancer. However, the role of NQO1 polymorphism in relation to carcinogenesis of cholangiocarcinoma (CCA), the most common liver cancer in the Northeast of Thailand, is unknown. Present study, we genotyped the NQO1 C609T polymorphism by PCR-RFLP in 210 CCA patients and 189 healthy control subjects matched for age, sex, and ethnicity. Among 189 Northeastern Thai healthy controls investigated, the NQO1 609T was present at 44% and the frequency distributions of C/C, C/T and T/T genotype were 32%, 53% and 15%, respectively. T allele frequency in the CCA patients was comparable with the healthy controls (p=0.4). In analysis for association of NQO1 genotype and survival time of the CCA patients at the time of diagnosis, the variant NQO1 genotypes (C/T and T/T) were not associated with lower survival time when compared with C/C genotype (p=0.092). Our findings suggested that NQO1 C609T polymorphism may not directly represent a genetic risk factor for CCA, however, the present study cannot exclude NQO1 as a possible modifier for CCA development. Further study in a larger population and biological function of NQO1 gene is required to verify the role of NQO1 in CCA.

127. CNS PENETRANT OR NOT? PITFALLS WITH IN VIVO DETERMINATION USING BRAIN TO BLOOD RATIO

Zigiang (Zack) Cheng[1], Jinqiang Zhang[1], Rongxia Liu[1], Yiwen Wu[1], Zhen Ge[1], Yi Li[1], Zong-ping Zhang[1], Yu Yang[1], Yan Chen[1], Hong Lu[1], Hans Hu[2], Barry Wang[2], Jason Meng[2], Raymond Zhao[2] and Eric Yang[1]
[1]Drug Metabolism and Pharmacokinetics, GlaxoSmithKline, Shanghai, China, 201203, [2]Neuroinflammation Discovery Performance Unit, GlaxoSmithKline, Shanghai, China, 201203

Purpose: The total brain to blood ratio (B/B) at single time point obtained from in vivo experiment has traditionally been used to determine whether a molecule is a CNS penetrant. Despite the effectiveness for


Proceedings of
31st Pharmacological and
Therapeutic Society of
Thailand Meeting
18-20 March 2009

Thai J Pharmacol Vol. 31, No.1, 2009 57

Original article **P05**

NAD(P)H-Quinone Oxidoreductase-1 (NQO1) C609T Genotypes in the Thai population

Pornsin Zeekpudsa[1], Auemduan Prawan[1*], Veerapol Kukongviriyapan[1] and Vajarabhongsa Bhudhisawasdi[2]

[1]Department of Pharmacology and [2]Department of Surgery, Faculty of Medicine, Liver Fluke and Cholangiocarcinoma Research Center, Khon Kaen University, Khon Kaen, Thailand, 40002

E-mail address: peuamd@kku.ac.th, auemduan@yahoo.com

Abstract

NAD(P)H-quinone oxidoreductase-1 (NQO1) is a detoxifying/antioxidant enzyme that plays a critical role in cellular defense against reactive oxygen species and toxic quinone derivatives, which in turn confer cytoprotection, inhibition of mutation and carcinogenesis. A polymorphism in human NQO1 at nucleotide position 609 (amino acid codon 187) is associated with diminished NQO1 enzymatic activity, and increased risk of chemically-induced cytoxicity and susceptibility to various forms of cancer. The purpose of this study was to determine the NQO1 polymorphism in the Thai population. We genotyped the NQO1 C609T polymorphism by PCR-RFLP in 189 unrelated healthy Thai subjects. The frequency of NQO1 C609 or wild type allele was 58.6%, where those of C/C, C/T and T/T genotypes were 32%, 53% and 15%, respectively. The frequency of NQO1 C609 allele in Thais was closely related to those observed in the East Asian (Oriental) population. Additionally, Thais exhibited a relatively low frequency of NQO1 C609 allele compared to Caucasian and African-American populations. Since, this is the first report on the NQO1 polymorphism in Thai population, data from this study can be use to further evaluate the impact of NQO1 polymorphism on susceptibility to chemically-induced toxicity and cancer risk.

Keywords: NAD(P)H-quinone oxidoreductase-1 (NQO1), Polymorphism, Thai population

Introduction

NAD(P)H:quinone oxidoreductase 1 (NQO1) is a detoxifying/antioxidant enzyme that plays an important role in protecting cells against chemically induced oxidative stress, cytotoxicity, mutagenicity, and carcinogenicity. NQO1 protects cells from oxidative damage by preventing the generation of reactive oxygen species and reactive electrophiles from certain environmental carcinogens (1). A genetic polymorphism (C→T) at nucleotide position 609 (amino acid codon 187) of the human NQO1 cDNA was show to reduce NQO1 enzyme activity, which may diminish the protection provided by NQO1. Variation in NQO1 enzyme activities has been suggested to influence an individual ability to metabolize carcinogenic agents and thus to be causally linked to cancer risk (2). Over years, a number of studies on the genetic polymorphism of NQO1 gene in many populations have been documented (4-7). However, no study has been reported on the genetic polymorphism of NQO1 gene in the Thai population. In the present investigation, efforts have been made to understand the genetic distribution of NQO1 polymorphism in Thai population.

CURRICULUM VITAE

Name: Miss Pornsin Zeekpudsa

Date of birth: 16th March 1985

Place of birth: Nakhon Ratchasima Province, Thailand

Education:

2003-2007 Bachelor Degree of Bachelor of Science (Medical Technology) Faculty of Associated medical science, Khon Kaen University

2007-2009 Graduate student for the degree of Master of Science program in Pharmacology, Faculty of Medicine, Khon Kaen University

Scholarships:

2008-2009 Liver Fluke and Cholangiocarcinoma Research Center