

## **REFERENCES**

1. Von Eschenbach A, Ho R, Murphy GP, Cunningham M, Lins N. American Cancer Society guideline for the early detection of prostate cancer: update. *Cancer J Clin* 1997; 47: 261-264.
2. Walker AR, Walker BF, Isaacson C, Doodha MJ, Segal I. Survival of Black men with prostatic cancer in Soweto, Johannesburg, South Africa. *J Urol* 1986; 135: 58-59.
3. Bratt O. Hereditary prostate cancer. *BJU Int* 2000; 85: 588-598.
4. Liu L, Cozen W, Bernstein L, Ross RK, Deapen D. Changing relationship between socioeconomic status and prostate cancer incidence. *J Natl Cancer Inst* 2001; 93: 705-709.
5. Huggins C, Stevens RE, Hodges CV. Studies on prostate cancer. *Arch Surg* 1941; 43:209-223.
6. Alberts B, Bray D, Lewis J, Raff M, Roberts K, Watson JD. Molecular Biology of the cell. Garland Publishing Inc. New York & London 1994; 1255-1294.
7. Rollerova E, Urbancikova M. Intracellular estrogen receptors, their characterization and function. *Endocrine Regulations* 2000; 34: 203-218.
8. Gronemeyer H, Benhamou B, Berry M, Bocquel MT, Gofflo D, Garcia T, Lerouge T, Metzger D, Meyer ME, Tora L, Vergezac A, Chambon P. Mechanisms of antihormone action. *J Steroid Biochem Molec Biol* 1992; 41: 217-221.
9. Enmark E, Gustafsson J-A. Oestrogen receptors – an overview. *J Int Med* 1999; 246: 133-138.
10. Kuiper GG, Enmark E, Pelto-Huikko M, Nilsson S, Gustaffson J-A. Cloning of a novel estrogen receptor expressed in rat prostate and ovary. *Proc Natl Acad Sci USA* 1996; 93: 5925-5930.
11. Mosselman S, Polman J, Dijkema R. ER $\beta$ : identification and characterization of a novel human estrogen receptor. *FEBS Lett* 1996; 392: 49-53.
12. Hakimi JM, Rondinelli RH, Schoenberg MP, Barrack ER. Androgen-receptor gene structure and function in prostate cancer. *World J Urol* 1996; 14: 329-337.
13. Griffiths K, Morton MS, Nicholson RI. Androgens, androgen receptors, antiandrogens and the treatment of prostate cancer. *Eur Urol* 1997; 32: 24-40.
14. Katzenellenbogen JA, O'Mally BW, Katzenellenbogen BS. Tripartite steroid hormone receptor pharmacology: interaction with multiple effector sites as a basis for the cell-



- and promoter-specific action of these hormones. Mol Endocrinol 1996; 10: 119-131.
15. Hyder SM, Chiapetta C, Stancel GM. Interaction of human estrogen receptors alpha and beta with the same naturally occurring estrogen response elements. Biochem Pharmacol 1999; 57: 597-601.
  16. Pennie WD, Aldridge TC, Brooks KN. Differential activation by xenoestrogens of ER alpha and ER beta when linked to different response elements. J Endocrinol 1998; 158: R11-R14.
  17. Pace P, Taylor J, Suntharalingam S, Coombes RC, Ali S. Human estrogen receptor beta binds DNA in a manner similar to and dimerizes with estrogen receptor alpha. J Clin Endocrinol Metab 1997; 82: 3509-3512.
  18. Ogawa S, Inoue S, Watanabe T, Hiroi H, Orimi A, Hosoi T, Ouchi Y, Muramatsu M. The complete primary structure of human estrogen receptor beta (hER beta) and its heterodimerization with ER alpha *in vivo* and *in vitro*. Biochem Biophys Res Commun 1998; 243: 122-126.
  19. Kuiper GG, Carlsson B, Grandien K, Enmark E, Hägglad J, Nilsson S, Gustaffson J-A. Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors  $\alpha$  and  $\beta$ . Endocrinol 1997; 138: 863-870.
  20. Kuiper GG, Lemmen JG, Carlsson B, Corton JC, Sage SH, Van der Saag PT, Van der Burg B, Gustaffson J-A. Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor  $\beta$ . Endocrinology 1998; 13: 4252-4263.
  21. Sun J, Meyers MJ, Fink BE, Rajendran R, Katzenellenbogen JA, Katzenellenbogen BS. Novel ligands that function as selective estrogens or antiestrogens for estrogen receptor-alpha or estrogen receptor-beta. Endocrinology 1999; 140: 800-804.
  22. McInerney EM, Weiss KE, Sun J, Mosselman S, Katzenellenbogen BS. Transcription activation by the human estrogen receptor subtype  $\beta$  (ER $\beta$ ) studied with ER $\beta$  and ER $\alpha$  receptor chimeras. Endocrinol 1998; 139: 4513-4522.
  23. Paech K, Webb P, Kuiper GGJM, Nilsson S, Gustafsson J, Kushner PJ, Scanlan TS. Differential ligand activation of estrogen receptors ER $\alpha$  and ER $\beta$  at AP1 sites. Science 1997; 277: 1508-1510.
  24. Déchaud H, Lejeune H, Garoscio-Cholet M, Mallein R, Pugeat M. Radioimmunoassay of testosterone not bound to sex-steroid-binding protein in plasma. Clin Chem 1989; 35: 1609-1614.
  25. Ekman P. The prostate as an endocrine organ: androgens and estrogens. Prostate 2000; 10: 14-18.
  26. Stone NN, Fair WR, Fishman J. Estrogen formation in human prostatic tissue from



- patients with and without benign prostatic hyperplasia. *Prostate* 1986; 9: 311-318.
27. Cooke PS, Young P, Hess RA, Cunha GR. Estrogen receptors expression in developing epididymis, efferent ductules and other male reproductive tracts. *Endocrinol* 1991; 128: 2874-2879.
  28. Hess RA, Bunick D, Lee K, Bahr J, Taylor JA, Korach KS, Lubahn DB. A role for oestrogens in the male reproductive system. *Nature* 1997; 390: 509-512.
  29. Simpson E. Local estrogen biosynthesis in males and females. *Endocrine-Related Cancer* 1999; 6: 131-137.
  30. Brinkmann AO, Jenster G, Kuiper GG, Ris C, van Laar JH, van der Korput JA, Degenhart HJ, Trifiro MA, Pinsky L, Romalo G. The human androgen receptor: structure/function relationship in normal and pathological situations. *J Steroid Biochem Mol Biol* 1992; 41: 361-368.
  31. Kuiper GG, Brinkmann AO. Phosphotryptic peptide analysis of the human androgen receptor: detection of a hormone-induced phosphopeptide. *Biochemistry* 1995; 34: 1851-1857.
  32. Van Laar JH, Berrevoets CA, Trapman J, Zegers ND, Brinkmann AO. Hormone dependent androgen receptor phosphorylation is accompanied by receptor transformation in human lymph node carcinoma of the prostate cells. *J Biol Chem* 1991; 266: 3734-3738.
  33. Luke MC, Coffey DS. The male sex accessory tissues: Structure, androgen action, and physiology. In: Knobil E, Niell JD, eds. *The physiology of reproduction*. New York: Raven Press; 1994; Vol 1: 1435-1488.
  34. Lipsett MB. Interaction of drugs, hormones and nutrition in the causes of cancer. *Cancer* 1979; 43: 1967-1981.
  35. Van Aswegen CH, Nieuwoudt LB, Van Rensburg HGJ, Steyn PL, Du Plessis DJ. Estradiol and cathecolestradiols as possible genotoxic carcinogens. *Clin Phys Biochem* 1989; 7: 34-39.
  36. Bosland MC, Dreef-Van Der Meulen HC, Sukumar S, Ofner P, Leav I, Han X, Liehr JG. Multistage prostate carcinogenesis: the role of hormones. *Princess Takamatsu Symp* 1991; 22: 109-123.
  37. Griffiths K. Estrogens and prostatic disease. *Prostate* 2000; 45: 87-100.
  38. Tenover JL. Testosterone and the ageing male. *J Androl* 1997; 18: 103-106.
  39. Stubbs AP, Murphy GM, Wilkinson ML. Isocratic high-performance liquid chromatographic measurement of optimal 5 $\alpha$ -steroid reductase activity in Hep-G2 cells. *J Chromatogr* 1991; 570: 293-299.



40. Wilding G. The importance of steroid hormones in prostate cancer. *Cancer Surv* 1992; 14: 113-130.
41. Wilson JD. The patogenesis of benign prostatic hyperplasia. *Am J Med* 1980; 68: 745-747.
42. Pincus SM, Mulligan T, Iranmanesh A, Gheorghui S, Godschalk M, Veldhuis JD. Older males secrete luteinizing hormone and testosterone more irregularly, and jointly more asynchronously than younger males. *Proc Natl Acad Sci USA* 1996; 93: 14100-14105.
43. Benbassat CA, Maki KC, Unterman TG. Circulating levels of insulin-like growth factor (IGF) binding protein-1 and -3 in aging men: relationships to insulin, glucose, and dehydroepiandrosterone sulfate levels and anthropometric measures. *J Clin Endocrinol Metab* 1997; 82: 1484-1491.
44. Prins GS, Sklarow RJ, Perschuck LP. Image analysis of androgen receptor immunostaining in prostate cancer accurately predicts response to hormonal therapy. *J Urol* 1998; 159: 641-649.
45. Peehl DM. Cellular biology of prostatic growth factors. *Prostate* 1996; 6: 74-78.
46. De Vere White R, Meyers F, Chi SG, Chamberlain S, Siders D, Lee F, Stewart S, Gumerlock PH. Human androgen receptor expression in prostate cancer following androgen ablation. *Eur Urol* 1997; 31: 1-6.
47. Hobisch A, Culig Z, Radmayr C, Bartsch G, Klocker H, Hittmair A. Distant metastasis from prostatic carcinoma express androgen receptor protein. *Cancer Res* 1995; 55: 3068-3072.
48. Hobisch A, Culig Z, Radmayr C, Bartsch G, Klocker H, Hittmair A. Androgen receptor status of lymph node metastases from prostate cancer. *Prostate* 1996; 28: 129-135.
49. Majumder PK, Wadhwa SN, Kumar VL. Androgen receptor transcript level in benign hypertrophy and carcinoma of the human prostate. *Urol Int* 1997; 59: 231-235.
50. Miyamoto KK, McSherry SA, Dent GA, Sar M, Wilson EM, French FS, Sharief Y, Mohler JL. Immunohistochemistry of the androgen receptor in human benign and malignant prostate tissue. *J Urol* 1993; 149: 1015-1019.
51. Magi-Galluzzi C, Xu X, Hlatky L, Hahnfeldt P, Kaplan I, Hsiao P, Chang C, Loda M. Heterogeneity of androgen receptor content in advanced prostate cancer. *Mod Pathol* 1997; 10: 839-845.
52. Stanford JL, Just JJ, Gibbs M, Wicklund KG, Neal CL, Blumenstein BA, Ostrander EA. Polymorphic repeats in the androgen receptor gene: molecular markers of prostate cancer risk. *Cancer Res* 1997; 57: 1194-1198.
53. Giovannucci E, Stampfer MJ, Krithivas K, Brown M, Dahl D, Brufsky A, Talcott J,



- Hennekens CH, Kantoff PW. The CAG repeat within the androgen receptor gene and its relationship to prostate cancer. *Proc Natl Acad Sci USA* 1997; 94: 3320-3323.
54. Hakimi JM, Schoenberg MP, Rondinelli RH, Piantadosi S, Barrack ER. Androgen receptor variants with short glutamine or glycine repeats may identify unique subpopulations of men with prostate cancer. *Clin Cancer Res* 1997; 3: 1599-1608.
55. Chamberlain NL, Driver ED, Miesfeld RL. The length and location of CAG trinucleotide repeats in the androgen receptor N-terminal domain affect transactivation function. *Nucleic Acid Res* 1994; 22: 3181-3186.
56. Irvine RA, Yu MC, Ross RK, Coetzee GA. The CAG and GGC microsatellites of the androgen receptor gene are in linkage disequilibrium in men with prostate cancer. *Cancer Res* 1995; 55: 1937-1940.
57. Edwards A, Hammond HA, Jin L, Caskey CT, Chakraborty R. Genetic variation at five trimeric and tetrameric tandem repeat loci in four human population groups. *Genomics* 1992; 12: 241-253.
58. Koivisto P, Kononen J, Palmberg C, Tammela T, Hytyinen E, Isola J, Trapman J, Cleutjens K, Noordzij A, Visakorpi T, Kallioniemi OP. Androgen receptor gene amplification: a possible molecular mechanism for androgen deprivation therapy failure in prostate cancer. *Cancer Res* 1997; 57: 314-319.
59. Koivisto P, Visakorpi T, Kallioniemi O. Androgen receptor gene amplification: A novel molecular mechanism for endocrine therapy resistance in human prostate cancer. *Scan J Clin Lab Invest Suppl* 1996; 226: 57-64.
60. Koivisto PA, Rantala I. Amplification of the androgen receptor gene is associated with P53 mutation in hormone-refractory recurrent prostate cancer. *J Pathol* 1999; 187: 237-241.
61. Kubota Y, Shuin T, Uemura H, Fujinami K, Miyoto H, Torigoe S, Dobashi Y, Kitamura H, Iwasaki Y, Danenberg K. Tumor suppressor gene p53 mutations in human prostate cancer. *Prostate* 1995; 27: 18-24.
62. Prinsloo SE, van Aswegen CH. The role of receptors in prostate cancer. *Adv Clin Chem* 2000; 36: 101-160.
63. Culig Z, Hobisch A, Cronauer MV, Radmayr C, Trapman J, Hittmair A, Bartsch G, Klocker H. Androgen receptor activation in prostatic tumor cell lines by insulin-like growth factor-1, keratinocyte growth factor and epidermal growth factor. *Cancer Res* 1995; 54: 5474-5478.
64. Nazareth LV, Weigel NL. Activation of the human androgen receptor through a protein kinase A signaling pathway. *J Biol Chem* 1996; 271: 19900-19907.



65. Reiniainen P, Palvimo JJ, Janne OA. Effects of mitogens on androgen receptor-mediated transactivation. *Endocrinol* 1996; 137: 4351-4357.
66. MacLean HE, Warne GL, Zajac JD. Localization of functional domains in the androgen receptor. *J Steroid Biochem Molec Biol* 1997; 62: 233-242.
67. Tilley WD, Buchanan G, Hickey TE, Bentel JM. Mutations in the androgen receptor gene are associated with progression of human prostate cancer to androgen independence. *Clin Cancer Res* 1996; 2: 277-285.
68. Culig Z, Hobisch A, Cronauer MV, Cato AC, Hittmair A, Radmayr C, Eberle J, Bartsch G, Klocker H. Mutant androgen receptor detected in an advanced-stage prostatic carcinoma is activated by adrenal androgens and progesterone. *Mol Endocrinol* 1993; 7: 1541-1550.
69. Elo JP, Harkonen P, Kyllonen AP, Lukkarinen O, Poutanen M, Vihko R, Vihko P. Loss of heterozygosity at 16q24.1-q24.2 is significantly associated with metastatic and aggressive behavior of prostate cancer. *Cancer Res* 1997; 7: 3356-3359.
70. Latil A. Loss of heterozygosity at chromosome 16q in prostate adenocarcinoma: identification of three independent regions. *Cancer Res* 1997; 57: 1058-1062.
71. Suzuki H, Akakura K, Komiya A, Aida S, Akimoto S, Shimazaki J. Codon 877 mutation in the androgen receptor gene in advanced prostate cancer: relation to antiandrogen withdrawal syndrome. *Prostate* 1996; 29: 153-158.
72. Newmark JR, Hardy DO, Tonb DC, Carter BS, Epstein JI, Isaacs WB, Brown TR, Barrack ER. Androgen receptor gene structure mutations in human prostate cancer. *Proc Natl Acad Sci USA* 1992; 89: 6319-6323.
73. Suzuki H, Sato N, Watabe Y, Masai M, Seino S, Shimazaki J. Androgen receptor gene mutations in human prostate cancer. *J Steroid Biochem Mol Biol* 1993; 46: 759-765.
74. Taplin ME, Bubley GJ, Shuster TD, Frantz ME, Spooner AE, Ogata GK, Keer HN, Balk SP. Mutation of the androgen-receptor gene in metastatic androgen-independent prostate cancer. *N Eng J Med* 1995; 332: 1393-1398.
75. Culig Z, Hobisch A, Peterziel H, Radmayr C, Bartsch G, Cato ACB, Klocker H. Hyperactive androgen receptor in prostate cancer: what does it mean for new therapy concepts? *Histol Histopathol* 1997; 12: 781-786.
76. Culig Z, Stober J, Gast A, Peterziel H, Hobisch A, Radmayr C, Hittmair A, Bartsch G, Cato AC, Klocker H. Activation of two mutant androgen receptors from human prostatic carcinoma by adrenal androgens and metabolic derivatives of testosterone. *Cancer Detect Prevent* 1996; 20: 68-75.
77. Gaddipati JP, McLeod DG, Heidenberg HB, Sesterhenn IA, Finger MJ, Moul JW,



- Srivastava S. Frequent detection of codon 877 mutation in the androgen receptor gene in advanced prostate cancers. *Cancer Res* 1994; 54: 2861-2864.
78. Barrett-Connor E, Garland C, McPhillips JB, Khaw KT, Wingard DL. A prospective, population-based study of androstenedione, estrogens, and prostatic cancer. *Cancer Res* 1990; 50: 169-173.
79. Veldscholte J, Berrevoets CA, Ris-Stalpers C, Kuiper GG, Jenster G, Trapman J, Brinkmann AO, Mulder E. The androgen receptor in LNCaP cells contains a mutation in the ligand binding domain which affects steroid binding characteristics and response to antiandrogens. *J Steroid Biochem Mol Biol* 1992; 41: 665-669.
80. Zhou ZX, Kempainen JA, Wilson EM. Identification of three proline-directed phosphorylation sites in the human androgen receptor. *Mol Endocrinol* 1995; 9: 605-605.
81. Klocker H, Neuschmid-Kaspar F, Culig Z, Cato AC, Hobisch A, Eberle J, Cronauer MV, Hittmair A, Radmayr C, Überreiter S. Androgen receptor alterations in patients with disturbances in male sexual development and in prostatic carcinoma. *Urol Int* 1995; 54: 2-5.
82. Yeh S, Miyamoto H, Shima H, Chang C. From estrogen to androgen receptor: a new pathway for sex hormones in prostate. *Proc Natl Acad Sci USA* 1998; 95: 5527-5532.
83. Fujimoto N, Yeh S, Kang HY, Inui S, Chang HC, Mizokami A, Chang C. Cloning and characterization of androgen receptor coactivator, ARA55, in human prostate. *J Biol Chem* 1999; 274: 8316-8321.
84. Yeh S, Lin HK, Kang HY, Thin TH, Lin MF, Chang C. From HER2/Neu signal cascade to androgen receptor and its coactivators: a novel pathway by induction of androgen target genes through MAP kinase in prostate cancer cells. *Proc Natl Acad Sci USA* 1999; 96: 5458-5463.
85. Yeh S, Miyamoto H, Nishimura K, Kang H, Ludlow J, Hsiao P, Wang C, Su C, Chang C. Retinoblastoma, a tumor suppressor, is a coactivator for the androgen receptor in human prostate cancer DU145 cells. *Biochem Biophys Res Comm* 1998; 248: 361-367.
86. Nakla AM, Romas NA, Rosner W. Estradiol activates the prostate androgen receptor and prostate-specific antigen secretion through the intermediacy of sex hormone-binding globulin. *J Biol Chem* 1997; 272: 6838-6841.
87. Castagnetta LA, Miceli MD, Sorci CMG, Pfeffer U, Farruggio R, Oliveri G, Calabro M, Carruba G. Growth of LNCaP human prostate cells is stimulated by estradiol via its own receptor. *Endocrinol* 1995; 136: 2309-2319.
88. Brolin J, Anderson L, Ekman P. Steroid receptor profile and receptors stability in



- subfractions of human prostate tissues. Critical aspects on microassays. *Urol Res* 1991; 19: 327-331.
89. Carrubba G, Pfeffer U, Fecarotta E, Coviello, DA, D'Amato E, Lo Castro M, Vidali G, Castagnetta L. Estradiol inhibits growth of hormone-nonresponsive PC3 human prostate cells. *Cancer Res* 1994; 54: 1190-1193.
90. Ekman P, Brolin J. Steroid receptor profile in human prostate cancer metastases as compared with primary prostatic carcinoma. *Prostate* 1991; 18: 147-153.
91. Ekman P, Barrack ER, Greene GL, Elwood VJ, Walsh PC. Estrogen receptors in human prostate: Evidence for multiple binding sites. *J Clin Endocrinol Metab* 1983; 57: 166-176.
92. Markaverich BM, Alejandro MA. Type II [<sup>3</sup>H]estradiol binding site antagonists: inhibition of normal and malignant prostate cell growth and proliferation. *Int J Oncol* 1998; 12: 1127-1135.
93. Viljoen TC, Van Aswegen CH, Du Plessis DJ. Binding of estradiol to whole prostatic DU-145 cells in the presence and absence of tamoxifen and acetylsalicylic acid. *Prostate* 1995; 27: 160-165.
94. Harper ME, Sibley PE, Francis AB, Nicholson RI, Griffiths K. Immunocytochemical assay for estrogen receptors applied to human prostatic tumors. *Cancer Res* 1986; 46: 4288s-4290s.
95. Hiramatsu M, Maehara I, Orikasa S, Sasano H. Immunolocalization of oestrogen and progesterone receptors in prostatic hyperplasia and carcinoma. *Histopathol* 1996; 28: 163-168.
96. Konishi N, Nakaoka S, Hiasa Y, Kitahori Y, Oshima M, Samma S, Okajima E. Immunohistochemical evaluation of estrogen receptor status in benign prostatic hypertrophy and in prostate carcinoma and the relationship to efficacy of endocrine therapy. *Oncol* 1993; 50: 259-263.
97. Kumar VL, Wadhwa SN, Kumar V, Farooq A. Androgen, estrogen, and progesterone receptor content and serum hormone profiles in patients with benign hypertrophy and carcinoma of the prostate. *J Surg Oncol* 1990; 44: 122-128.
98. Brolin J, Skoog L, Ekman P. Immunohistochemistry and biochemistry in detection of androgen, progesterone, and estrogen receptors in benign and malignant human prostatic tissue. *Prostate* 1992; 20: 281-295.
99. Khalid BA, Nurshireen A, Rashidah M, Zainal BY, Roslan BA, Mahamooth Z. Steroid hormone receptors in prostatic hyperplasia and prostatic carcinoma. *Med J Malaysia* 1990; 45: 148-153.



100. Emtage LA, Dunn PJ, Rowse AD. Androgen and oestrogen receptor status in benign and neoplastic prostate disease. Study of prevalence and influence on time to progression and survival in prostate cancer treated by hormone manipulation. Br J Urol 1989; 63: 627-633.
101. Hobisch A, Hittmair A, Daxenbichler G, Wille S, Radmayr C, Hobisch-Hagen P, Bartsch G, Klocker H, Culig Z. Metastatic lesions from prostate cancer do not express oestrogen and progesterone receptors. J Pathol 1997; 182: 356-361.
102. Nativ O, Umehara T, Colvard DS, Therneau TM, Farrow GM, Spelsberg TC, Lieber MM. Relationship between DNA ploidy and functional estrogen receptors in operable prostate cancer. Eur Urol 1997; 32: 96-99.
103. Dhom G, Seitz G, Wermert N. Histology and immunohistochemistry studies in prostate cancer. Am J Clin Oncol 1988; 11: S37-S42.
104. Ehara H, Koji T, Deguchi T, Yoshii A, Nakano M, Nakane PK, Kawada Y. Expression of estrogen receptor in diseased human prostate assessed by non-radioactive *in situ* hybridization and immunohistochemistry. Prostate 1995; 27: 304-313.
105. Kruithof-Dekker TG, Tetu B, Janssen PJ, Van der Kwast TH. Elevated estrogen receptor expression in human prostatic stromal cells by androgen ablation therapy. J Urol 1996; 156: 1194-1197.
106. Wermert N, Gerdes J, Loy V, Seitz G, Scherr O, Dhom G. Investigations of the estrogen (ER-ICA-test) and the progesterone receptor in the prostate and prostatic carcinoma on immunohistochemical basis. Virch Arch [A] 1988; 412: 387-391.
107. Dunning WF. Prostatic cancer in the rat. Monogr Natl Cancer Inst 1963; 12: 351-369.
108. Mobbs BG, Johnson IE, DeSombre ER, Toth J, Hughes A. Regulation of estrogen and progestin receptor concentrations in an experimental rat prostatic carcinoma by estrogen, antiestrogen, and progesterone. Cancer Res 1987; 47: 2645-2651.
109. Chang WY, Prins GS. Estrogen receptor- $\beta$ : Implications for the prostate gland. Prostate 1999; 40: 115-124.
110. Enmark E, Pelto-Huikko M, Grandien K, Lagercrantz S, Lagercrantz J, Fried G, Nordenskjöld M, Gustaffson J-A. Human estrogen receptor  $\beta$ -gene structure, chromosomal localization, and expression pattern. J Clin Endocrinol Metab 1997; 82: 4258-4265.
111. Hanstein B, Liu H, Yancisin MC, Brown M. Functional analysis of novel estrogen receptor- $\beta$  isoforms. Mol Endocrinol 1999; 13: 129-137.
112. Prins GS, Marmer M, Woodham C, Chang W, Kuiper G, Gustafson J-A, Birch L. Estrogen receptor- $\beta$  messenger ribonucleic acid ontogeny in the prostate of normal



and neonatally estrogenized rats. *Endocrinol* 1998; 139: 874-883.

113. Shughue PJ, Lane MV, Scrimo PJ, Merchenthaler I. Comparative distribution of estrogen receptor-alpha (ER-alpha) and beta (ER-beta) mRNA in the rat pituitary, gonad, and reproductive tract. *Steroids* 1998; 63: 498-504.
114. Montano MM, Jaiswal AK, Katzenellenbogen BS. Transcriptional regulation of the muna quinone reductase gene by antiestrogen-ligated estrogen receptor- $\alpha$  and estrogen receptor- $\beta$ . *J Biol Chem* 1998; 273: 25443-25449.
115. Chang WY, Prins GS. Estrogen receptor- $\beta$ : Implications for the prostate gland. *Prostate* 1999; 40: 115-124.
116. Garnick MB. The dilemmas of prostate cancer. *Sci Am* 1994; 270: 52-59.
117. Kokontis J, Takakura K, Hay N, Liao S. Increased androgen receptor acitivity and altered c-myc expression in prostate cancer cells after long-term androgen deprivation. *Cancer Res* 1994; 54: 1566-1573.
118. Mahler C, Verhelst J, Denis L. Clinical pharmacokinetics of the antiandrogens and their efficacy in prostate cancer. *Clin Pharmacokinet* 1998; 34: 405-417.
119. Trachtenberg J. Innovative approaches to the hormonal treatment of advanced prostate cancer. *Eur Urol* 1997; 32: 78-80.
120. US Department of Health and Human Services. Relative effectiveness and cost-effectiveness of methods of androgen suppression in the treatment of advanced prostate cancer. Agency for Health Care Policy and Research, Evidence Report/Technology Assessment 1999; 4: 1-6.
121. Kuil CW, Brinkmann AO. Androgens, antiandrogens and androgen receptor abnormalities. *Eur Urol* 1996; 29: 78-82.
122. Hedlund PO, Jacobsson H, Vaage S, Hahne B, Sandin T, Kontturi M, Nordlie O, Espoti P. Treatment of high-grade, high stage prostate cancer with estramustine phosphate or diethylstibesterol. A double-blind study. The SPCG-1 Study Group. Scandinavian Prostate Cancer Group. *Scand J Urol Nephrol* 1997; 31: 167-172.
123. Kitahara S, Yoshida K, Ishizaka K, Kageyama Y, Kawakami S, Tsujii T, Oshima H. Stronger suppression of serum testosterone and FSH levels by a synthetic estrogen than by castration or an LH-RH agonist. *Endocr J* 1997; 44: 527-532.
124. McLeod DG, Crawford ED, DeAntoni EP. Combined androgen blockade: The gold standard for metastatic prostate cancer. *Eur Urol* 1997; 32: 70-77.
125. Robertson CN, Roberson KM, Padilla GM, O'Brien ET, Cook JM, Kim CS, Fine RL. Induction of apoptosis by diethylstilbestrol in hormone-insensitive prostate cancer cells. *J Natl Cancer Inst* 1996; 88: 908-917.



126. Damber JE, Landström M, Bergh A, Tomic R. The effects of castration, testosterone and oestrogen on epithelial and stromal growth and morphology of the Dunning (R3327H) prostatic adenocarcinoma. *Scand J Urol Nephrol Suppl* 1988; 110: 145-148.
127. Stephens FO. Phytoestrogens and prostate cancer: possible preventative role. *Med J Aust* 1997; 167: 138-140.
128. Zhou JR, Gugger ET, Tanaka T, Guo Y, Blackburn GL, Clinton SK. Soybean phytochemicals inhibit the growth of transplantable human prostate carcinoma and tumor angiogenesis in mice. *J Nutr* 1999; 129: 1628-1635.
129. Santibanez JF, Navarro A, Martinez J. Genistein inhibits proliferation and *in vitro* invasive potential of human prostatic cancer cell lines. *Anticancer Res* 1997; 17: 1199-1204.
130. Rosenberg Zand RS, Jenkins DJ, Diamandis EP. Genistein: a potent natural antiandrogen. *Clin Chem* 2000; 46: 887-888.
131. Pandian SS. Fatty acids and prostate cancer: current status and future challenges. *JR Coll Surg Edeinb* 1999; 44: 352-361.
132. Purasiri P, Heys S, Eremin O. Essential fatty acids and malignant disease. *Eur J Surg Onc* 1994; 20: 603-606.
133. Horrobin DF. Unsaturated Lipids and Cancer. In: Horrobin DF, ed. *New Approaches to Cancer Treatment. Unsaturated lipids and Photodynamic Therapy*. NY: Churchill Communications Europe 1994; 3-29.
134. Horrobin DF, Manku MS. Clinical biochemistry of essential fatty acids. In: Horrobin DF, ed. *Omega-6 Essential Fatty Acids. Pathophysiology and Roles in Clinical Medicine*. NY: Alan R Liss 1990; 21-53.
135. Cunnane SC. The conditional nature of the dietary need for polyunsaturates: a proposal to reclassify 'essential fatty acids' as 'conditionally-indespensable' or 'conditionally-dispensable' fatty acids. *Br J Nutr* 2000; 84: 803-812.
136. Alberts B, Bray D, Lewis J, Raff M, Roberts K, Watson JD. *Molecular Biology of the cell*. Garland Publishing Inc. New York & London 1994; 477-479.
137. Sinclair HM. History of essential fatty acids. In: Horrobin DF, ed. *Omega-6 Essential Fatty Acids. Pathophysiology and Roles in Clinical Medicine*. NY: Alan R Liss 1990; 21-53.
138. Byers T, Giesecker K. Issues in the design and interpretation of studies of fatty acids and cancer in humans. *Am J Clin Nutr* 1997; 66: 1541S-1547S.
139. Godley PA, Campbell MK, Miller C, Gallagher P, Martinson FE, Mohler JL, Sandler RS. Correlation between biomarkers of omega-3 fatty acid consumption and



- questionnaire data in African American and Caucasian United States males with and without prostatic carcinoma. *Cancer Epidemiol Biomarkers Prev* 1996; 5: 115-119.
140. Carroll KK, Khor HT. Dietary fat in relation to tumorigenesis. *Prog Biochem Pharmacol* 1975; 10: 308-353.
  141. Giovannucci E. Epidemiologic characteristics of prostate cancer. *Cancer* 1995; 75: 1766-1777.
  142. Wang Y, Corr jG, Thaler HT, Tao Y, Fair WR, Heston WD. Decreased growth of established human prostate LNCaP tumors in nude mice fed a low-fat diet. *J Natl Cancer Inst* 1995; 87: 1456-1462.
  143. Haenzel W, Kurihara M. Studies of Japanese migrants. I. Mortality from cancer and other diseases among Japanese in the United states. *J Natl Cancer Inst* 1968; 40: 43-68.
  144. Staszewski W, Haenzel W. Cancer among the Polish-born in the United States. *J Natl Cancer Inst* 1965; 35: 291-297.
  145. Erasmus U. *Fats that Heal. Fats that Kill.* Burnaby BC Canada. Alive Books 1993; 362-369.
  146. Motaung E, Prinsloo SE, van Aswegen CH, du Toit PJ, Becker PJ, du Plessis DJ. Cytotoxicity of combined essential fatty acids on a human prostate cancer cell line. *Prostaglandins Leukot Essent Fatty Acids* 1999; 61: 331-337.
  147. Whittemore AS, Kolonel LN, Wu AH, John EM, Gallagher RP, Howe GR, Burch JD, Hankin J, Dreon DM, West DW. Prostate cancer in relation to diet, physical activity, and body size in blacks, whites, and Asians in the United States and Canada. *J Natl Cancer Inst* 1995; 87: 652-661.
  148. Gann PH, Hennekens CH, Sacks FM, Grodstein F, Giovannucci EL, Stampfer MJ. Prospective study of plasma fatty acids and risk of prostate cancer. *J Natl Cancer Inst* 1994; 86: 281-286.
  149. Giovannucci E, Rimm EB, Colditz GA, Stampfer MJ, Ascherio A, Chute CC, Willet WC. A prospective study of dietary fat and risk of prostate cancer. *J Natl Cancer Inst* 1993; 85: 1571-1579.
  150. Walker ARP, Walker BF, Tsotsetsi NG, Sebitso C, Siwedi D, Walker AJ. Case-control studies on control study of prostate cancer in black patients in Soweto, South Africa. *Br J Cancer* 1992; 65: 438-441.
  151. West DW, Slattery MLI, Robison LM, French TK, Mahoney AW. Adult dietary intake and prostate cancer risk in Utah: a case-control study with special emphasis on aggressive tumors. *Cancer Causes Control* 1991; 2: 85-94.



152. Schuurman AG, van den Brandt PA, Dorant E, Brants HA, Goldbohm RA. Association of energy and fat intake with prostate carcinoma risk: Results from The Netherlands Cohort Study. *Cancer* 1999; 86: 1019-1027.
153. Terry P, Lichtenstein P, Feychting M, Ahlbom A, Wolk A. Fatty fish consumption and risk of prostate cancer. *Lancet* 2001; 357: 1764-1766.
154. Norrish AE, Skaeff CM, Arribas GL, Sharpe SJ, Jackson RT. Prostate cancer risk and comsumption of fish oils: a dietary biomarker-based case-control study. *Br J Cancer* 1999; 81: 1238-1242.
155. Harvei S, Bjerve KS, Tretli S, Jellum E, Robsahm TE, Vatten L. Prediagnostic level of fatty acids in serum phospholipids: omega-3 and omega-6 fatty acids and the risk of prostate cancer. *Int J Cancer* 1997; 71: 545-551.
156. Bakker N, van't Veer P, Zock PL. Adipose fatty acids and cancers of the breast, prostate and colon: an ecological study. EURAMIC study group. *Int J Cancer* 1997; 72: 587-591.
157. Kaul L, Heshmat MY, Kovi J, Jackson MA, Jackson AG, Jones GW, Edson M, Enterline JP, Worrell RG, Perry SL. The role of diet in prostate cancer. *Nutr Cancer* 1987; 9: 123-128.
158. Mishina T, Watanabe H, Araki H, Nakao M. Epidemiological study of prostatic cancer by matched-pair analysis. *Prostate* 1985; 6: 423-436.
159. Royai R, Lange RH, Vessella R. Preclinical models of prostate cancer. *Sem Oncol* 1996; 23: 35-40.
160. Waters DJ, Sakr WA, Hayden DW, Land CM, McKinney L, Murphy GP, Radinsky R, Ramoner R, Richardson RC, Tindall DJ. Workgroup 4: spontaneous prostate carcinoma in dogs and nonhuman primates. *Prostate* 1998; 36: 64-67.
161. Sharma P, Schreiber-Agus N. Mouse models of prostate cancer. *Oncogene* 1999; 18: 5349-5355.
162. Williams JH. The use of gamma linolenic acid and natural vitamin E for the treatment of multicentric lymphoma in two dogs. *J S Afr Vet Assoc* 1998; 59: 141-144.
163. Griffiths G, Jones HE, Eaton CL, Stobart AK. Effect of n-6 polyunsaturated fatty acids on growth and lipid composition of neoplastic and non-neoplastic canine prostate epithelial cell cultures. *Prostate* 1997; 31: 29-36.
164. Maini A, Archer C, Wang CY, Haas GP. Comparative pathology of benign prostatic hyperplasia and prostate cancer. *In Vivo* 1997; 11: 293-299.
165. Pylkkanen L, Makela S, Santti R. Animal models for the preneoplastic lesions of the prostate. *Eur Urol* 1996; 30: 243-248.



166. Lucia MS, Bostwick DG, Bosland M, Cockett A, Knapp DW, Leav I, Pollard M, Rinker-Schaeffer C, Shirai T, Watkins BA. Workgroup I: Rodent models of prostate cancer. *Prostate* 1996; 36: 49-55.
167. Levine AJ. Tumor suppressor genes. *Bioessays* 1990; 12: 60-66.
168. Zhou J-R, Blackburn GL. Bridging animal and human studies: what are the missing segments in dietary fat and prostate cancer? *Am J Clin Nutr* 1997; 66: 1572S-1580S.
169. Karmali RA, Reichel P, Cohen LA, Terano T, Hirai A, Tamura Y, Yoshida S. The effects of dietary omega-3 fatty acids on the DU-145 transplantable human prostatic tumor. *Anticancer Res* 1987; 7: 1173-1179.
170. Rose DP, Cohen LA. Effects of dietary menhaden oil and retinol acetate on the growth of DU-145 human prostatic adenocarcinoma cells transplanted into athymic nude mice. *Carcinogenesis* 1988; 9: 603-605.
171. Cesano A, Visonneau S, Scimeca JA, Kritchevsky D, Santoli D. Opposite effects of linoleic acid and conjugated linoleic acid on human prostatic cancer in SCID mice. *Anticancer Res* 1998; 18: 1429-1434.
172. Du Toit PJ, Van Aswegen CH, DJ Du Plessis. The effect of essential fatty acids on growth and urokinase-type plasminogen activator production in human prostate DU-145 cells. *Prostaglandins Leukot Essent Fatty Acids* 1996; 55: 173-177.
173. Martnett LJ. Generation of mutagens during arachidonic acid metabolism. *Cancer Metastasis Rev* 1994; 13: 303-308.
174. Dempke W, Rie C, Grothey A, Schmoll H-J. Cyclooxygenase-2: a novel target for cancer chemotherapy? *J Cancer Res Clin Oncol* 2001; 127: 411-417.
175. Horrobin DF. Essential Fatty Acids, Lipid Peroxidation, and Cancer. In: Horrobin DF, ed. *Omega-6 Essential Fatty Acids. Pathophysiology and Roles in Clinical Medicine*. NY: Alan R Liss 1990; 351-377.
176. Bostwick DG, Alexander EE, Singh R, Shan A, Qian J, Santella RM, Oberley LW, Yan T, Zhong W, Jiang X, Oberley TD. Antioxidant enzyme expression and reactive oxygen species damage in prostatic intraepithelial neoplasia and cancer. *Cancer* 2000; 89: 123-134.
177. Das UN, Begin ME, Ells G. Fatty acid changes during the induction of differentiation of human promyelocytic leukemia (HL-60) cells by phorbolmyristate acetate. *Prostaglandins Leukot Essent Fatty Acids* 1992; 46: 235-239.
178. Oberley TD, Zhong W, Szweda LI, Oberley LW. Localization of antioxidant enzymes and oxidative damage products in normal and malignant prostate epithelium. *Prostate* 2000; 44: 144-155.



179. Das UN, Madhavi N, Sravan Kumar G, Padma M, Sangeetha P. Can tumour cell drug resistance be reversed by essential fatty acids and their metabolites? *Prostaglandins Leukot Essent Fatty Acids* 1998; 58: 39-54.
180. Burns C P, Spector A. Membrane fatty acid modification in tumor cells: a potential therapeutic adjunct. *Lipids* 1987; 22: 178-184.
181. Van Aswegen CH, du Plessis DJ. A possible role for enzymes in tumor cell invasion. *Med Hyp* 1997; 48: 443-447.
182. Liu XH, Rose DP. Suppression of type IV collagenase in MDA-MB-435 human breast cancer cells by eicosapentaenoic acid *in vitro* and *in vivo*. *Cancer Lett* 1995; 92: 21-26.
183. Nunez EA. Free fatty acids as modulators of the steroid hormone message. *Prostaglandins Leukot Essent Fatty Acids* 1993; 48: 63-70.
184. Sumida C, Gruber R, Nunez E. Role of fatty acids in signal transduction: modulators and messengers. *Prostaglandins Leukot Essent Fatty Acids* 1993; 48: 117-122.
185. O'Brain CA. Protein kinase C-alpha: a novel target for the therapy of androgen-independent prostate cancer? *Oncol Rep* 1998; 5: 305-309.
186. Liang T, Liao S. Inhibition of steroid 5 alpha-reductase by specific aliphatic unsaturated fatty acids. *Biochem J* 1992; 285: 557-562.
187. Wang X, Walsh LP, Stocco DM. The role of arachidonic acid on LH-stimulated steroidogenesis and steroidogenic acute regulatory protein accumulation in MA-10 mouse Leydig tumor cells. *Endocrine* 1999; 10: 7-12.
188. Mele PG, Dada LA, Paz C, Neuman I, Cymering CB, Mendez CF, Finkelstein CV, Cornejo Maciel F, Podesta EJ. Involvement of arachidonic acid and the lipoxygenase pathway in mediating luteinizing hormone-induced testosterone synthesis in rat Leydig cells. *Endocrine Res* 1997; 23:15-26.
189. Martin ME, Vranckx R, Benassayag C, Nunez EA. Modifications of the properties of human sex-steroid protein by nonestified fatty acids. *J Biol Chem* 1986; 261: 2954-2959.
190. Martin ME, Benassayag C, Nunez EA. Selective changes in binding and immunological properties of human corticosteroid binding globulin by free fatty acids. *Endocrinol* 1988; 123: 1178-1186.
191. Vallette G, Christeff N, Bogard C, Benassayag C, Nunez EA. Dynamic pattern of estradiol binding to uterine receptors of the rat: inhibition and stimulation by unsaturated fatty acids. *J Biol Chem* 1988; 263: 3639-3645.
192. Benassayag C, Vallette G, Hassid J, Raymond JP, Nunez EA. Potentiation of estradiol



- binding to human tissue proteins by unsaturated nonestrified fatty acids. *Endocrinol* 1986; 118: 1-7.
193. Kato J. Arachidonic acid as a possible modulator of estrogen, progestin, androgen, and glucocorticoid receptors in the central and peripheral tissues. *J Steroid Biochem* 1989; 34: 219-227.
194. Hwang PLH. Interactions of unsaturated fatty acids with anti-estrogen-binding sites. *Biochem J* 1987; 243: 359-364.
195. Mitshuhashi N, Kato J. Modulation of steroid hormone receptors in the brain. Inhibitory effect of fatty acids on the binding of androgen receptor and R1881. *Enocrinol Jpn* 1988; 35: 93-96.
196. Mooradian AD, Pamplona DM, Viosca SP, Korenman SG. Effect of free fatty acids on the bioavailability of plasma testosterone and dihydrotestosterone. *J Steroid Biochem* 1988; 29: 369-370.
197. Vallette G, Vanet A, Sumida C, Nunez EA. Modulatory effects of unsaturated fatty acids on the binding of glucocorticoid to rat liver glucocorticoid receptors. *Endocrinol* 1991; 129: 1363-1369.
198. Kenny FS, Gee JM, Nicholson RI, Ellis IO, Morris TM, Watson SA, Bryce RP, Robertson JF. Effect of dietary GLA+/- tamoxifen on the growth, ER expression and fatty acid profile of ER positive human breast cancer xenografts. *Int J Cancer* 2001; 92: 342-347.
199. Brawer MK. Prostate-specific antigen: current status. *CA Cancer J Clin* 1999; 49: 264-281.
200. Hanchette CL, Schwartz GG. Geographic patterns of prostate cancer mortality: Evidence for a protective effect of ultraviolet radiation. *Cancer* 1992; 70: 2861-2869.
201. Feldman D, Skowronski RJ, Peehl DM. Vitamin D and prostate cancer. *Adv Exp Med Biol* 1995; 375: 53-63.
202. Gann PH, Ma J, Hennekens CH, Hollins BW, Haddad JG, Stampfer MJ. Circulating vitamin D metabolites in relation to subsequent development of prostate cancer. *Cancer Epidemiol Biomarkers Prev* 1996; 5: 121-126.
203. Chan JM, Stampfer MJ, Ma J, Rimm EB, Willett WC, Giovannucci EL. Supplemental vitamin E intake and prostate cancer risk in a large cohort of men in the United States. *Cancer Epidemiol Biomarkers Prev* 1999; 8: 893-899.
204. Giles G, Ireland P. Diet, nutrition and prostate cancer. *Int J Cancer Suppl* 1997; 10: 13-17.
205. Giovannucci E, Ascherio A, Rimm EB, Stampfer MJ, Golditz GA, Willet WC. Intake of



- carotenoids and retinol in relation to risk of prostate cancer. *J Natl Cancer Inst* 1995; 87: 1767-1776.
206. Giovannucci E, Clinton SK. Tomatoes, lycopene, and prostate cancer. *Proc Soc Exp Biol Med* 1998; 218: 129-139.
207. Lui XH, Wiley HS, Meikle AW. Androgens regulate proliferation of human prostate cancer cells in culture by increasing transforming growth factor- $\alpha$  (TGF- $\alpha$ ) and epidermal growth factor (EGF)/TGF- $\alpha$  receptor. *J Clin Endocrinol Metab* 1993; 77: 1472-1478.
208. Heshmat MY, Kaul L, Kovi J, Jackson MA, Jackson AG, George WJ, Edson M, Enterline JP, Worrell RG, Perry SL. Nutrition and prostate cancer: a case-control study. *Prostate* 1985; 6: 7-17.
209. Willet WC. Specific fatty acids and risks of breast and prostate cancer: dietary intake. *Am J Clin Nutr* 1997; 66: 1577S-1563S.
210. Booyens J, Engelbrecht P, Le Roux S, Louwrens CC. Some effects of the essential fatty acids linoleic acid and alpha-linolenic acid and of their metabolites gamma-linolenic acid, arachidonic acid, eicosapentaenoic acid, docosahexaenoic acid, and of prostaglandins A<sub>2</sub> and E<sub>1</sub> on the proliferation of human osteogenic sarcoma cells in culture. *Prostaglandins Leukot Medicine* 1984; 15: 15-33.
211. Das UN. Gamma-linolenic acid, arachidonic acid, and eicosapentaenoic acid as potential anticancer drugs. *Nutrition* 1990; 6: 429-434.
212. Mengeaud V, Nano JL, Fournel S, Rampal P. Effects of eicosapentaenoic acid, gamma-linolenic acid and prostaglandin E<sub>1</sub> on three human colon carcinoma cell lines. *Prostaglandins Leukot Essent Fatty Acids* 1992; 47: 313-319.
213. Rose DP. Effects of dietary fatty acids on breast and prostate cancers: evidence from *in vitro* experiments and animal studies. *Am J Clin Nutr* 1997; 66: 1513S-1522S.
214. Horrobin DF. The role of essential fatty acids and prostaglandins in the premenstrual syndrome. *J Reprod Med* 1983; 28: 465-468.
215. Kruger MC, Coetzer H, de Winter R, Gericke G, van Papendorp DH. Calcium, gamma-linolenic acid and eicosapentaenoic acid supplementation in senile osteoporosis. *Aging (Milano)* 1998; 10: 385-394.
216. Ho S-M, Damassa D, Kwan PWL, Seto HSK, Leav I. Androgen receptor levels and androgen contents in the prostate lobes of intact and testosterone-treated noble rats. *J Androl* 1985; 6: 279-290.
217. Culig Z, Hobisch A, Hittmair A, Peterziel H, Cato ACB, Bartsch G, Klocker H. Expression, structure, and function of androgen receptor in advanced prostatic

- carcinoma. *The Prostate* 1998; 35: 63-70.
218. Wolf RM, Schneider SL, Pontes JE, Englander L, Karr JP, Murphy GP, Sandberg A. Estrogen and progestin receptors in human prostatic carcinoma. *Cancer* 1985; 55: 2477-2481.
219. Klocker H, Culig Z, Kaspar F, Hobisch A, Eberle J, Reissigl A, Bartsch G. Androgen signal transduction and prostatic carcinoma. *World J Urol* 1994; 12: 99-103.
220. Castagnetta LAM, Giuseppe C. Letter to the editor. Metastatic lesions from prostate cancer do not express oestrogen and progesterone receptors. *J Path* 1998; 185: 435-437.
221. Fleshner NE, Klotz LH. Diet, androgens, oxidative stress and prostate cancer susceptibility. *Cancer Metastasis Rev* 1998-99; 17: 325-30.
222. Turcotte G, Chapdelaine A, Roberts KD, Chevalier S. Androgen binding as evidenced by a whole cell assay system using cultured canine prostatic epithelial cells. *J Steroid Biochem* 1988; 29: 69-76.
223. Scatchard G. The attraction of proteins for small molecules and ions. *Ann NY Acad Sci* 1949; 51: 660-672.
224. Clark JH, Mani SK. Actions of Ovarian Steroid Hormones. In: *The Physiology of Reproduction*, E Knobil, JD Niell, eds. Raven Press, New York 1994; Vol 1: 1011-1059.
225. Brooks SC, Locke ER, Soule H. Estrogen receptor in human cell line (MCF-7) from breast carcinoma. *J Biol Chem* 1973; 248: 6251-6253.
226. Osborne CK, Hobbs K, Trent JM. Biological differences among MCF-7 human breast cancer cell lines from different laboratories. *Breast Cancer Res Treatm* 1987; 9: 111-121.
227. Ogawa S, Inoue S, Watanabe T, Orimo A, Hosoi T, Ouchi Y, Muramatsu M. Molecular cloning and characterization of human estrogen receptor betacx: a potential inhibitor of estrogen action in human. *Nucleic Acids Res* 1998; 26: 3505-3512.
228. Katsuoka Y, Hoshino H, Shiramizu M, Sakabe K, Seiki K. Autoradiographic and cytochemical localization of androgen in human prostatic cancer cell lines. *Urol* 1986; 28: 228-231.
229. Castagnetta L, Carruba G, Fecarotta E, Lo Casto M, Cusimano R, Pavone-Macaluso M. Soluble and nuclear type I and II androgen-binding sites in benign hyperplasia and cancer of the human prostate. *Urol Res* 1992; 20: 127-132.
230. Lamarre D, Chevalier S, McKercher G, Bleau G, Roberts KD, Chapdelaine A. Quantification of cytosolic steroid receptors in secretory and non-secretory epithelial

- cells of the canine prostate. *J Steroid Biochem* 1985; 22: 1-7.
231. Delos S, lehle C, Martin PM, Raynaud JP. Inhibition of the activity of 'basic' 5  $\alpha$ -reductase (type I) detected in DU-145 cells and expressed in insect cells. *J Steroid Biochem Mol Biol* 1994; 48: 347-352.
232. Robinette CL, Blume CD, Mawhinney MG. Androphilic and estrophilic molecules in canine prostate glands. *Invest Urol* 1978; 15: 425-431.
233. Castagnetta L, Granata OM, Polito L, Blasi L, Cannella S, Carruba G. Different conversion metabolic rates of testosterone are associated to hormone-sensitive status and response of human prostate cancer cells. *J Steroid Biochem Mol Biol* 1994; 49: 351-357.
234. Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ. Prospective study of sex hormone levels and risk of prostate cancer. *J Natl Cancer Inst* 1996; 88: 1118-1126.
235. Borrás M, Leclercq G. Modulatory effect of nonestrified fatty acids on structure and binding characteristics of estrogen receptor from MCF-7 cells. *J Recept Res* 1992; 12: 463-484.
236. Segal IH. Biochemical Calculations 2<sup>nd</sup> ed. John Wiley & Sons. New York 1976: 208-323.
237. Powell C E, Soto A, Sonnenschein C. Identification and characterization of membrane estrogen receptor from MCF-7 estrogen-target cells. *J Steroid Biochem Mol Biol* 2001; 77: 97-108.
238. Benten WP, Lieberherr M, Giese G, Wrehlike C, Stamm O, Sekeris CE, Mossmann H, Wunderlich F. Functional testosterone receptors in plasma membranes of T cells. *FASEB J* 1999; 13: 123-133.
239. Armen TA, Gay CV. Simultaneous detection and functional response of testosterone and estradiol receptors in osteoblast plasma membranes. *J Cell Biochem* 2000; 79: 620-627.
240. Powell IJ. Prostate cancer in the African American: Is this a different disease? *Sem Urol Oncol* 1998; 16: 221-226.
241. Taipale J, Beachy PA. The hedgehog and Wnt signalling pathways in cancer. *Nature* 2001; 411: 349-354.
242. Wade PA. Transcriptional control at regulatory checkpoints by histone deacetylases: molecular connections between cancer and chromatin. *Hum Mol Gen* 2001; 10: 693-698.
243. Evan GI, Vousden KH. Proliferation, cell cycle and apoptosis in cancer. *Nature* 2001; 411: 342-348.



244. Baylin SB, Esteller M, Rountree MR, Bachman KE, Schuebel K, Herman JG. Aberrant patterns of DNA methylation, chromatin formation and gene expression in cancer. *Hum Mol Gen* 2001; 10: 687-692.
245. Shay JW, Zou Y, Hiyama E, Wright WE. Telomerase and cancer. *Hum Mol Gen* 2001; 10: 677-685.
246. Mohaghegh P, Hickson ID. DNA helicase deficiencies associated with cancer predisposition and premature ageing disorders. *Hum Mol Gen* 2001; 10: 741-746.
247. Ponder BAJ. Cancer genetics. *Nature* 2001; 411: 336-341.
248. Ravindranath N, Ioffe SL, Marshall GR, Ramaswamy S, Plant TM, Dym M. Androgen depletion activates telomerase in the prostate of the nonhuman primate, Macaca mulatta. *Prostate* 2001; 49: 79-89.
249. Clarke SD, Jump DB. Dietary polyunsaturated fatty acid regulation of gene transcription. *Annu Rev Nutr* 1994; 14: 83-98.
250. Pizer ES, Pflug BR, Bova GS, Han WF, Udan MS, Nelson JB. Increased fatty acid synthase as a therapeutic target in androgen-independent prostate cancer progression. *Prostate* 2001; 47: 102-110.
251. Blake WL, Clarke SD. Suppression of hepatic fatty acid synthase and S14 gene transcription by dietary polyunsaturated fat. *J Nutr* 1990; 120: 1727-1729.
252. Clarke SD, Armstrong MK, Jump DB. Nutritional control of rat liver fatty acid synthase and S14 mRNA abundance. *J Nutr* 1990; 120: 218-224.
253. Jump DB, Bell A, Santiago V. Polyunsaturated fatty acids inhibit S14 gene transcription in rat liver and cultured hepatocytes. *Proc Natl Acad Sci USA* 1993; 90: 8454-8458.
254. Nakamura I, Kimijima I, Zhang GJ, Onogi H, Endo Y, Suzuki S, Tuchiya A, Takenoshita S, Kusakabe T, Suzuki T. Fatty acid synthase expression in Japanese breast carcinoma patients. *Int J Mol Med* 1999; 4: 381-387.
255. Oskouian B. Overexpression of fatty acid synthase in SKBR3 breast cancer cell line is mediated via a transcriptional mechanism. *Cancer Lett* 2000; 149: 43-51.
256. Alo PL, Visca P, Trombetta G, Mangoni A, Monaco S, Botti C, Serpieri DE, Di Tondo U. Fatty acid synthase (FAS) predictive in poorly differentiated early breast carcinomas. *Tumori* 1999; 85: 35-40.
257. Myers RB, Oelschlager DK, Weiss HL, Frost AR, Grizzle WE. Fatty acid synthase: an early molecular marker of progression of prostatic adenocarcinoma to androgen independence. *J Urol* 2001; 165: 1027-1032.

258. Chirgwin JM, Przybyla AE, MacDonald RJ, Rutter WJ. Isolation of biologically active ribonucleic acid from sources enriched in ribonuclease. *Biochemistry* 1979; 18: 5294-5299.
259. Blumberg DD. Creating a ribonuclease-free environment. *Methods in Enzymology* 1987; 152: 20-24.
260. Chomczynski P. A reagent for the single-step simultaneous isolation of RNA, DNA and proteins from cell and tissue samples. *Biotechniques*. 1993; 15: 532-534.
261. Chomczynski P, Sacchi N. Single-step method of RNA isolation by acid guanidinium thiocyanate-phenol-chloroform extraction. *Anal Biochem* 1987; 162: 156-159.
262. Thorpe GHG, Kricka LJ, Moseley SB, Whitehead TP. Phenols as enhancers of the chemiluminescent horseradish peroxidase-luminol-hydrogen peroxide reaction: Application in luminescence-monitored enzyme immunoassays. *Clin Chem* 1985; 31: 1335-1341.
263. Trayhurn P, Duncan JS, Nestor A, Thomas MEA, Rayner DV. Chemiluminescent detection of mRNAs on Northern blots with Digoxigenin end-labeled oligonucleotides. *Anal Bioch* 1994; 222: 224-230.
264. Sambrook J, Fritsch EF, Maniatis T. Molecular Cloning: A laboratory manual, Cold Spring Harbor Laboratory, Cold Spring Harbor 1989; 7.3.
265. Beckman WC Jr, Stumpf WE, Sar M. Localization of steroid hormones and their receptors. A comparison of autoradiographic and immunocytochemical techniques. In: Bullock, Petrusz P, eds. *Techniques in immunocytochemistry Volume II*. Academic Press Limited, London 1983: 25-37.
266. Walker RA. The localization of receptors and binding sites with reference to steroids. In: Polak JM, van Noorden S, eds. *Immunocytochemistry: Modern methods and applications 2<sup>nd</sup> ed.* John Wright & Sons Ltd. Bristol 1986: 188-197.
267. Bevitt DJ, Milton ID, Piggot N, Henry L, Carter MJ, Toms GL, Lennard TWJ, Westly B, Angus B, Horne CHW. New monoclonal antibodies to oestrogen and progesterone receptors effective for paraffin section immunohistochemistry. *J Pathol* 1997; 183: 228-232.
268. Gusterson BA, Monaghan P. Immunocytochemistry of cell lines. In: Polak JM, van Noorden S, eds. *Immunocytochemistry: Modern methods and applications 2<sup>nd</sup> ed.* John Wright & Sons Ltd. Bristol 1986: 261-272.
269. Press MF, Xu S, Wang J, Greene GL. Subcellular distribution of estrogen receptor and progesterone receptor with and without specific ligand. *Am J Pathol* 1989; 135: 857-864.



270. Van Noorden S. Tissue preparation and immunostaining techniques for light microscopy. In: Polak JM, van Noorden S, eds. Immunocytochemistry: Modern methods and applications 2<sup>nd</sup> ed. John Wright & Sons Ltd. Bristol 1986: 27-53.
271. Leathem A. Lectin Histochemistry. In: Polak JM, van Noorden S, eds. Immunocytochemistry: Modern methods and applications 2<sup>nd</sup> ed. John Wright & Sons Ltd. Bristol 1986: 167-187.
272. Steiner MS, Gingrich JR. Gene therapy for prostate cancer: where are we now? *J Urol* 2000; 164: 1121-1136.
273. Eder IE, Culig Z, Ramoner R, Thurnher M, Putz T, Nessler-Menardi C, Tiefenthaler M, Bartsch G, Klocker H. Inhibition of LNCaP prostate cancer cells by means of androgen receptor antisense oligonucleotides. *Cancer Gene Ther* 2000; 7: 997-1007.
274. Anderson WF. Human gene therapy. *Nature* 1998; 392: 25-30.
275. Chambers G, Lawrie L, Cash P, Murray GI. Proteomics: a new approach to the study of disease. *J Pathol* 2000; 192: 280-288.
276. Ornstein DK, Gillespie JW, Paweletz CP, Durray PH, Herring J, Vocke CD, Topalian SL, Bostwick DG, Linehan WM, Petricoin EF 3<sup>rd</sup>, Emmert-Buck MR. Proteonomic analysis of laser capture microdissected human prostate cancer and in vitro prostate cell lines. *Electrophoresis* 2000; 21: 2235-2242.
277. Dhanasekaran SM, Barrette TR, Ghosh D, Shah R, Varambally S, Kurachi K, Pienta KJ, Rubin MA, Chinnaiyan AM. Delineation of prognostic biomarkers in prostate cancer. *Nature* 2001; 412(6849): 822-826.
278. Latil A, Bièche I, Vidaud D, Lidereau R, Berthon P, Cussenot O, Vidaud M. Evaluation of androgen, estrogen (ER $\alpha$  and ER $\beta$ ), and progesterone receptor expression in human prostate cancer by real-time quantitative reverse transcription-polymerase chain reaction assays. *Cancer Res* 2001; 61: 1919-1926.
279. Pasquali D, Rossi V, Esposito D, Abbondanza C, Puca GA, Bellastella A, Sinisi AA. Loss of estrogen receptor  $\beta$  expression in malignant human prostate cells in primary cultures and in prostate cancer tissues. *J Clin Endocrinol Metab* 2001; 86: 2051-2055.
280. Vladusic EA, Hornby AE, Guerra-Vladusic FK, Lakins J, Lupu R. Expression and regulation of estrogen receptor  $\beta$  in human breast tumors and cell lines. *Oncol Rep* 2000; 7: 157-167.
281. Stoica A, Saceda M, Doraiswamy VI, Coleman C, Martin MB. Regulation of estrogen receptor- $\alpha$  gene expression by epidermal growth factor. *J Endocrinol* 2000; 165: 371-378.
282. Donaghue C, Westly BR, May FE. Selective promoter usage of the human estrogen



- receptor- $\alpha$  gene and its regulation by estrogen. *Mol Endocrinol* 1999; 13: 1934-1950.
283. Koibuchi Y, Iino Y, Uchida T, Andoh T, Horii Y, Nagasawa M, Horiguchi J, Maemura M, Takei H, Yokoe T, Morishita Y. Regulation of estrogen receptors and epidermal growth factor receptor by tamoxifen under high and low estrogen environments in MCF-7 cells grown in athymic mice. *Oncol Rep* 2000; 7: 135-140.
284. Grant ES, Batchelor KW, Habib FK. Androgen independence of primary epithelial cultures of the prostate is associated with a down-regulation of the androgen receptor gene expression. *Prostate* 1996; 29: 339-349.
285. Waller AS, Sharrard RM, Berthon P, Maitland NJ. Androgen receptor localization and turnover in human prostate epithelium treated with the antiandrogen, casodex. *J Mol Endocrinol* 2000; 24: 339-351.
286. Li LC, Chui R, Nakajima K, Oh BR, Au HC, Dahiya R. Frequent methylation of estrogen receptor in prostate cancer: correlation with tumor progression. *Cancer Res* 2000; 60: 702-706.
287. Chlenski A, Nakashiro K, Ketels KV, Korovaitseva GI, Oyasu R. Androgen receptor expression in androgen-independent prostate cancer cell lines. *Prostate* 2001; 47: 66-75.
288. Ailhaud G. Regulation of gene expression by fatty acids in the adipose cell. *Prostaglandins Leukot Essent Fatty Acids* 1993; 48: 89-90.
289. Hughes-Fulford M, Chen Y, Tjandrawinata RR. Fatty acid regulates gene expression and growth of human prostate cancer PC-3 cells. *Carcinogenesis* 2001; 22: 701-707.
290. Armstrong MK, Blake WL, Clarke SD. Arachidonic acid suppression of fatty acid synthase gene expression in cultured rat hepatocytes. *Biochem Biophys Res Commun* 1991; 177: 1056-1061.
291. Kachhap SK, Dange P, Nath Gosh S. Effect of omega-6 polyunsaturated fatty acid (linoleic acid) on BRCA1 gene expression in MCF-7 cell line. *Cancer Lett* 2000; 154: 115-120.
292. Park W, Choi, J-J, Hwang E-S, Lee J-H. Identification of a variant estrogen receptor lacking exon 4 and its coexpression with wild-type estrogen receptor in ovarian carcinomas. *Clin Cancer Res* 1996; 2: 2029-2035.
293. Berthois Y, Katzenellenbogen JA, Katzenellenbogen BS. Phenol red in tissue culture media is a weak estrogen: Implications concerning the study of estrogen-responsive cells in culture. *Proc Natl Acad Sci USA* 1986; 83: 2496-2500.
294. Moreno-Cuevas JE, Sirbasku DA. Estrogen mitogenic action. III. Is phenol red a "red herring"? *In Vitro Cell Dev Biol Anim* 2000; 36: 447-464.



295. Murphy LC, Dotzlaw H, Leygue E, Douglas D, Coutts A, Watson PH. Estrogen receptor variants and mutations. *J Steroid Biochem Mol Biol* 1997; 62: 363-372.
296. Ye Q, Chung LW, Cinar B, Li S, Zhai HE. Identification and characterization of estrogen receptor variants in prostate cancer cell lines. *J Steroid Biochem Mol Biol* 2000; 75: 21-31.
297. Ramesh G, Das UN, Koratkar R, Padma M, Sagar PS. Effect of essential fatty acids on tumor cells. *Nutrition*. 1992; 8: 343-347.
298. Verhoeven G, Swinnen JV. Indirect mechanisms and cascades of androgen action. *Mol Cell Endocrinol*. 1999; 151: 205-212.
299. Van Voorst F, de Kruijff B. Role of lipids in the translocation of proteins across membranes. *Biochem J* 2000; 347: 601-612.
300. O'Neil JS, Burow ME, Green AE, McLachlan JA, Henson MC. Effects of estrogen on leptin gene promoter activation in MCF-7 breast cancer and JEG-3 choriocarcinoma cells: selective regulation via estrogen receptors alpha and beta. *Mol Cell Endocrinol* 2001; 176: 67-75.
301. Eriksson E, Sundblad C, Lisjo P, Modigh K, Andersch B. Serum levels of androgens are higher in women with premenstrual irritability and dysphoria than in controls. *Psyconeuroendocrinol* 1992; 17: 195-204.
302. Korhonen S, Saarijarvi S, Aito M. Successful estradiol treatment of psychotic symptoms in the premenstrual phase: a case report. *Acta Psychiatr Scand* 1995; 92: 237-238.
303. Smith RN, Studd JW, Zamblera D, Holland EF. A randomised comparison over eight months of 100 micrograms twice weekly doses of transdermal oestradiol in the treatment of severe premenstrual syndrome. *Br J Obstet Gynaecol* 1995; 102: 475-484.
304. Horrobin DF. The role of essential fatty acids and prostaglandins in the premenstrual syndrome. *J Reprod Med* 1983; 28: 465-468.
305. Britton KT, Koob GF. Premenstrual steroids? *Nature* 1998; 392: 869-70.
306. Brush MG, Watson SJ, Horrobin DF, Manku MS. Abnormal essential fatty acid levels in plasma of women with premenstrual syndrome. *Am J Obstet Gynecol* 1984; 150: 363-366.
307. Bunyavejchevin S, Limpaphayom KK. The metabolic and bone density effects of continuous combined 17-beta estradiol and norethisterone acetate treatments in Thai postmenopausal women: a double-blind placebo-controlled trial. *J Med Ass Thailand* 2001; 84: 45-53.



308. Schlemmer CK, Coetzer H, Claassen N, Kruger MC. Oestrogen and essential fatty acid supplementation corrects bone loss due to ovariectomy in the female Sprague Dawley rat. *Prostaglandins Leukot Essent Fatty Acids* 1999; 61: 381-390.
309. Newman PE, Alzheimer's disease revisited. *Med Hypoth* 2000; 54: 774-776.
310. Surai PF, Noble RC, Sparks NH, Speake BK. Effect of long-term supplementation with arachidonic or docosahexaenoic acids on sperm production in the broiler chicken. *J Reprod Fert*. 2000; 120: 257-264.
311. Ware JL. Growth factor network disruption in prostate cancer progression. *Cancer Metastasis Rev* 1999; 17: 443-447.
312. Niederberger C. Computational tools for the modern andrologist. *J Androl* 1996; 17: 462-466.
313. Douglas TH, Moul JW. Applications of neural networks in urologic oncology. *Semin Urol Oncol* 1998; 16: 35-39.
314. Tewari A, Narayan P. Novel staging tool for localized prostate cancer: a pilot study using genetic adaptive neural networks. *J Urol* 1998; 160: 430-436.
315. Vawer A, Rashbass J. The biological toolbox a computer program for simulating basic biological and pathological processes. *Comput Methods Programs Biomed* 1997; 52: 203-211.
316. Endy D, Brent R. Modeling cellular behaviour. *Nature* 2001; 409: 391-395.
317. Peto J. Cancer epidemiology in the last century and the next decade. *Nature* 2001; 411: 390-395.
318. Minh TB, Watanabe M, Tanabe S, Yamada R, Hata J, Watanabe S. Occurrence of Tris (4-chlorophenyl) methane, tris (4-chlorophenyl) methanol, and some other persistent organochlorides in Japanese human adipose tissue. *Environ Health Perspect* 2000; 108: 599-603.
319. Lebeuf M, Bernt KE, Noel M, Hammill MO, Measures L. Tris (4-chlorophenyl) methane and tris (4-chlorophenyl) methanol in marine mammals from the Estuary and Gulf of St Lawrence. *Environ Pollut* 2001; 111: 29-43.
320. Chevrier J, Dewailly E, Ayotte P, Mauriege P, Despres JP, Tremblay A. Body weight loss increases plasma and adipose tissue concentrations of potentially toxic pollutants in obese individuals. *Int J Obes Relat Metab Disord* 2000; 24: 1272-1278.
321. Aronson KJ, Miller AB, Woolcot CG, Sterns EE, McCready DR, Lickley LA, Fish EB, Hiraki GY, Holloway C, Ross T, Hanna WM, SenGupta SK, Weber JP. Breast adipose tissue concentrations of polychlorinated biphenyls and other organochlorines and breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 2000; 9: 55-63.



322. Slim R, Hammock BD, Toborek M, Robertson LW, Newman LW, Morisseau CH, Watkins BA, Saraswathi V, Hennig B. The role of methyl-linoleic acid epoxide and diol metabolites in the amplified toxicity of linoleic acid and polychlorinated biphenyls to vascular endothelial cells. *Toxicol Appl Pharmacol* 2001; 171: 184-193.
323. Frenoux JM, Prost ED, Belleville JL, Prost JL. A polyunsaturated fatty acid diet lowers blood pressure and improves antioxidant status in spontaneously hypertensive rats. *J Nutr* 2001; 131: 39-45.