

- by surface enhanced laser desorption/ionization mass spectrometry. *J Urol*, 174: 1213–1217, 2005.
28. Fujii K, Kondo T, Yokoo H, Yamada T, Matsuno Y, Iwatsuki K, Hirohashi S. Protein expression pattern distinguishes different lymphoid neoplasms. *Proteomics*, 5: 4274–4286, 2005.
29. Hayashida Y, Honda K, Osaka Y, Hara T, Umaki T, Tsuchida A, Aoki T, Hirohashi S, Yamada T. Possible prediction of chemoradiosensitivity of esophageal cancer by serum protein profiling. *Clin Cancer Res*, 11: 8042–8047, 2005.
30. Honda K, Hayashida Y, Umaki T, Okusaka T, Kosuge T, Kikuchi S, Endo M, Tsuchida A, Aoki T, Itoi T, Moriyasu F, Hirohashi S, Yamada T. Possible detection of pancreatic cancer by plasma protein profiling. *Cancer Res*, 65: 10613–10622, 2005.
31. Katoh H, Shibata T, Kokubu A, Ojima H, Fukayama M, Kanai Y, Hirohashi S. Epigenetic instability and chromosomal instability in hepatocellular carcinoma. *Am J Pathol*, 168: 1375–1384, 2006.
32. Fujii K, Kondo T, Yokoo H, Okano T, Yamada M, Yamada T, Iwatsuki K, Hirohashi S. Database of two-dimensional polyacrylamide gel electrophoresis of proteins labeled with CyDye DIGE Fluor saturation dye. *Proteomics*, 6: 1640–1653, 2006.
33. Katoh H, Shibata T, Kokubu A, Ojima H, Kosuge T, Kanai Y, Hirohashi S. Genetic inactivation of the APC gene contributes to the malignant progression of sporadic hepatocellular carcinoma: A case report. *Gene Chrom Cancer*, 45: 1050–1057, 2006.
34. Okano T, Kondo T, Fujii K, Nishimura T, Takano T, Ohe Y, Tsuta K, Matsuno Y, Gemma A, Kato H, Kudoh S, Hirohashi S. Proteomic signature corresponding to the response to gefitinib (Iressa, ZD1839), an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor in lung adenocarcinoma. *Clin Cancer Res*, 13: 799–805, 2007.
35. Okano T, Kondo T, Kakisaka T, Fujii K, Yamada M, Kato H, Nishimura T, Gemma A, Kudoh S, Hirohashi S. Plasma proteomics of lung cancer by a linkage of multi-dimensional liquid chromatography and two-dimensional difference gel electrophoresis. *Proteomics*, 6: 3938–3948, 2006.
36. Suehara Y, Kondo T, Fujii K, Hasegawa

- T, Kawai A, Seki K, Beppu Y,  
Nishimura T, Kurosawa H, Hirohashi  
S. Proteomic signatures  
corresponding to histological  
classification and grading of  
soft-tissue sarcomas. *Proteomics*,  
6: 4402-4409, 2006.
37. Fujii K, Kondo T, Yamada M, Iwatsuki  
K, Hirohashi S. Toward a  
comprehensive quantitative  
proteome database: proteome  
expression map of lymphoid  
neoplasms by 2-D DIGE and MS.  
*Proteomics*, 6: 4856-4876, 2006.
38. Hatakeyama H, Kondo T, Fujii K,  
Nakanishi Y, Kato H, Fukuda S,  
Hirohashi S. Protein clusters  
associated with carcinogenesis,  
histological differentiation and  
nodal metastasis in esophageal  
cancer. *Proteomics*, 6: 6300-6316,  
2006.
39. Ono M, Shitashige M, Honda K, Isobe  
T, Kuwabara H, Matsuzaki H,  
Hirohashi S, Yamada T. Label-free  
quantitative proteomics using large  
peptide data sets generated by  
nanoflow liquid chromatography and  
mass spectrometry. *Mol Cell*  
*Proteomics*, 5: 1338-1347, 2006.
40. Loukopoulos P, Shibata T, Katoh H,  
Kokubu A, Sakamoto M, Yamazaki K,  
Kosuge T, Kanai Y, Hosoda F, Imoto  
I, Ohki M, Inazawa J, Hirohashi S.  
Genome-wide array-based  
comparative genomic hybridization  
analysis of pancreatic  
adenocarcinoma: Identification of  
genetic indicators that predict  
patient outcome. *Cancer Sci*, 98:  
392-400, 2007.
41. Kondo T, Hirohashi S. Application of  
highly sensitive fluorescent dyes  
(CyDye DIGE Fluor Saturation Dye) to  
laser microdissection and  
two-dimensional difference gel  
electrophoresis (2D-DIGE) for  
cancer proteomics. *Nat Protocol*,  
1: 2940-2956, 2007.
42. Shitashige M, Naishiro Y, Idogawa M,  
Honda K, Ono M, Hirohashi S, Yamada  
T. Involvement of Splicing Factor-1  
in  $\beta$ -Catenin/T Cell  
Factor-4-mediated Gene  
Transactivation and Pre-mRNA  
Splicing. *Gastroenterology*, in  
press.
43. Hara T, Honda K, Shitashige M, Ono M,  
Matsuyama H, Naito K, Hirohashi S,  
Yamada T. Mass spectrometry  
analysis of the native protein  
complex containing actinin-4 in  
prostate cancer cells. *Mol Cell*  
*Proteomics*, in press.
44. Idogawa M, Masutani M, Shitashige M,  
Honda K, Tokino T, Shinomura Y, Imai

- K, Hirohashi S, Yamada T. Ku70 and poly(ADP-ribose) polymerase-1 competitively regulate  $\beta$ -catenin and T-cell factor-4-mediated gene transactivation: Possible linkage of DNA damage recognition and Wnt signaling. *Cancer Res*, in press.
45. Wenlin Du, Hattori Y, Hashiguchi A, Kondoh K, Hozumi N, Ikeda Y, Sakamoto M, Hata J, Yamada T. Tumor angiogenesis in the bone marrow of multiple myeloma patients and its alteration by thalidomide treatment. *Pathol Int*, 54: 285-294, 2004.
46. Chuma M, Saeki N, Yamamoto Y, Ohta T, Asaka M, Hirohashi S, Sakamoto M. Expression profiling in hepatocellular carcinoma with intrahepatic metastasis: identification of high-mobility group I (Y) protein as a molecular marker of hepatocellular carcinoma metastasis. *Keio J Med*, 53: 90-97, 2004.
47. Koide N, Yamada T, Shibata R, Mori T, Fukuma M, Yamazaki K, Aiura K, Shimazu M, Hirohashi S, Nimura Y, Sakamoto M. Establishment of perineural invasion models and analysis of gene expression revealed an invariant chain (CD74) as a possible molecule involved in perineural invasion in pancreatic cancer. *Clin Cancer Res*, 12: 2419-2426, 2006.
48. Shibata R, Mori T, Du W, Chuma M, Gotoh M, Shimazu M, Ueda M, Hirohashi S, Sakamoto M. Overexpression of cyclase-associated protein 2 in multistage hepatocarcinogenesis. *Clin Cancer Res*, 12: 5363-5368, 2006.
49. Haga K, Ohno S, Yugawa T, Narisawa-Saito M, Fujita M, Sakamoto M, Galloway DA, Kiyono T. Efficient immortalization of primary human cells by p16INK4a-specific short hairpin RNA or Bmi-1, combined with introduction of hTERT. *Cancer Sci*, 98: 147-154, 2007.
50. Higashiguchi A, Yamada T, Susumu N, Mori T, Suzuki A, Aoki D, Sakamoto M. Specific expression of hepatocyte nuclear Factor-1 $\beta$  in the ovarian clear cell adenocarcinoma and its application to cytological diagnosis. *Cancer Sci*, in press.
51. Sanada T, Yokoi S, Arii S, Yasui K, Imoto I, Inazawa J. Skp2 overexpression is a p27Kip1-independent poor prognosticator in patients with

- biliary tract cancers. *Cancer Sci*, 95: 969-976, 2004.
52. Tanami H, Imoto I, Hirasawa A, Yuki Y, Sonoda I, Inoue J, Yasui K, Misawa-Furihata A, Kawakami Y, Inazawa J. Involvement of overexpressed wild-type BRAF in the growth of malignant melanoma cell lines. *Oncogene*, 23: 8796-8804, 2004.
53. Misawa A, Hosoi H, Imoto I, Iehara T, Sugimoto T, Inazawa J. Translocation (1;22) (p36;q11.2) with concurrent del(22) (q11.2) resulted in homozygous deletion of SNF5/INI1 in a newly established cell line derived from extrarenal rhabdoid tumor. *J Hum Genet*, 49: 586-589, 2004.
54. Inazawa J, Inoue J, Imoto I. Comparative genomic hybridization (CGH) arrays pave the way for identification of novel cancer-related genes. *Cancer Sci*, 95: 559-563, 2004.
55. Yokoi S, Yasui K, Mori M, Iizasa T, Fujisawa T, Inazawa J. Amplification and overexpression of SKP2 are associated with metastasis of non-small-cell lung cancers to lymph nodes. *Am J Pathol*, 165: 175-180, 2004.
56. Inoue J, Otsuki T, Hirasawa A, Imoto I, Matsuo Y, Shimizu S, Taniwaki M, Inazawa J. Overexpression of PDZK1 within the 1q12-q22 amplicon is likely to be associated with drug-resistance phenotype in multiple myeloma. *Am J Pathol*, 165: 71-81, 2004.
57. Yuki Y, Imoto I, Imaizumi M, Hibi S, Kaneko Y, Amagasa T, Inazawa J. Identification of a novel fusion gene in a pre-B acute lymphoblastic leukemia with t(1;19) (q23;p13). *Cancer Sci*, 95: 503-507, 2004.
58. Sonoda I, Imoto I, Inoue J, Shibata T, Shimada Y, Chin K, Imamura M, Amagasa T, Gray JW, Hirohashi S, Inazawa J. Frequent silencing of low density lipoprotein receptor-related protein 1B (LRP1B) expression by genetic and epigenetic mechanisms in esophageal squamous-cell carcinoma. *Cancer Res*, 64: 3741-3747, 2004.
59. Yasui K, Mihara S, Zhao C, Okamoto H, Saito-Ohara F, Tomida A, Funato T, Yokomizo A, Naito S, Imoto I, Tsuruo T, Inazawa J. Alteration in copy numbers of genes as a mechanism for acquired drug resistance. *Cancer Res*, 64: 1403-1410, 2004.
60. Takada H, Imoto I, Tsuda H, Nakanishi Y, Ichikura T, Mochizuki H,

- Mitsufuji S, Hosoda F, Hirohashi S, Ohki M, Inazawa J. ADAM23, a possible tumor suppressor gene, is frequently silenced in gastric cancers by homozygous deletion or aberrant promoter hypermethylation. *Oncogene*, 24: 8051-8060, 2005.
61. Misawa A, Inoue J, Sugino Y, Hosoi H, Sugimoto T, Hosoda F, Ohki M, Imoto I, Inazawa J. Methylation-associated silencing of the nuclear receptor 1I2 gene in advanced-type neuroblastomas, identified by bacterial artificial chromosome array-based methylated CpG island amplification. *Cancer Res*, 65: 10233-10242, 2005.
62. Saigusa K, Hashimoto N, Tsuda H, Yokoi S, Maruno M, Yoshimine T, Aoyagi M, Ohno K, Imoto I, Inazawa J. Overexpressed Skp2 within 5p amplification detected by array-based comparative genomic hybridization is associated with poor prognosis of glioblastomas. *Cancer Sci*, 96: 676-683, 2005.
63. Tanami H, Tsuda H, Okabe S, Iwai T, Sugihara K, Imoto I, Inazawa J. Involvement of cyclin D3 in liver metastasis of colorectal cancer, revealed by genome-wide copy-number analysis. *Lab Invest*, 85: 1118-1129, 2005.
64. Tanaka E, Hashimoto Y, Ito T, Okumura T, Kan T, Watanabe G, Immamura M, Inazawa J, Shimada Y. The clinical significance of Aurora-A/STK15/BTAK expression in human esophageal squamous cell carcinoma. *Clin Cancer Res*, 11: 1827-1834, 2005.
65. Izumi H, Inoue J, Yokoi S, Hosoda H, Shibata T, Sunamori M, Hirohashi S, Inazawa J, Imoto I. Frequent silencing of DBC1 is by genetic or epigenetic mechanisms in non-small cell lung cancers. *Hum Molec Genet*, 14: 997-1007, 2005.
66. Takada H, Imoto I, Tsuda H, Sonoda I, Ichikura T, Mochizuki H, Okanoue T, Inazawa J. Screening of DNA copy-number aberrations in gastric cancer cell lines by array-based comparative genomic hybridization. *Cancer Sci*, 96: 100-110, 2005.
67. Imoto I, Izumi H, Yokoi S, Hosoda H, Shibata T, Hosoda F, Ohki M, Hirohashi S, Inazawa J. Frequent silencing of the candidate tumor suppressor PCDH20 by epigenetic mechanism in non-small-cell lung cancers. *Cancer Res*, 66: 4617-4626, 2006.
68. Kumada K, Yao R, Kawaguchi T, Karasawa M, Hoshikawa Y, Ichikawa K, Sugitani Y, Imoto I, Inazawa J.

- Sugawara M, Yanagida M, Noda T. The selective continued linkage of centromeres from mitosis to interphase in the absence of mammalian separase. *J Cell Biol*, 172: 835-846, 2006.
69. Nakada S, Katsuki Y, Imoto I, Yokoyama T, Nagasawa M, Inazawa J, Mizutani S. Early G2/M checkpoint failure as a molecular mechanism underlying etoposide-induced chromosomal aberrations. *J Clin Invest*, 116: 80-89, 2006.
70. Kozaki K, Imoto I, Pimkhaokham A, Hasegawa S, Tsuda H, Omura K, Inazawa J. PIK3CA mutation is an oncogenic aberration at advanced stages of oral squamous cell carcinoma. *Cancer Sci*, 97: 1351-1358, 2006.
71. Takada H, Imoto I, Tsuda H, Nakanishi Y, Sakakura C, Mitsufuji S, Hirohashi S, Inazawa J. Genomic loss and epigenetic silencing of very low density lipoprotein receptor involved in gastric carcinogenesis. *Oncogene*, 25: 6554-6562, 2006.
72. Nakagawa T, Pimkhaokham, A, Suzuki E, Omura K, Inazawa J, Imoto I. Genetic or epigenetic silencing of low density lipoprotein receptor-related protein 1B expression in oral squamous cell carcinoma. *Cancer Sci*, 97: 1070-1074, 2006.
73. Saigusa K, Imoto I, Tanikawa C, Aoyagi M, Ohno K, Nakamura Y, Inazawa J. RGC32, a novel p53-inducible gene, is located on centrosomes during mitosis and results in G2/M arrest. *Oncogene*, 26: 1110-1121, 2007.
74. Yu W, Imoto I, Inoue J, Onda M, Emi M, Inazawa J. A novel amplification target, DUSP26, promotes anaplastic thyroid cancer cell growth by inhibiting p38 MAPK activity. *Oncogene*, 26: 1178-1187, 2007.
75. Surace EI, Murakami Y, Scheithauer BW, Perry A, Gutmann DH. Tumor Suppressor in Lung Cancer-1 (TSLC1) expression is lost in sporadic meningioma. *J Neuropathol Exp Neurol*, 63: 1015-1027, 2004.
76. Lung HL, Cheng Y, Kumaran MK, Liu E, TB, Murakami Y, Chan CY, Yau WL, Stanbridge EJ, Lung ML. Fine mapping of 11q22-23 tumor suppressive region and involvement of TSLC1 in nasopharyngeal carcinoma. *Int J Cancer*, 112: 628-635, 2004.
77. Saino M, Maruyama T, Sekiya T, Kayama T, Murakami Y. Inhibition of

- angiogenesis in human glioma cell lines by antisense RNA from the soluble guanylate cyclase genes, GUCY1A3 and GUCY1B3. *Oncol Rep*, 12: 7-52, 2004.
78. Murakami Y, Isogai K, Tomita H, Sakurai-Yageta M, Maruyama T, Hidaka A, Nose K, Sugano K, Kaneko A. Detection of allelic imbalance in the gene expression of hMSH2 or RB1 in lymphocytes from pedigrees of hereditary non-polyposis colorectal cancer and retinoblastoma by an RNA difference plot. *J Hum Genet*, 49: 635-641, 2004.
79. Masuda M, Kikuchi S, Maruyama T, Sakurai-Yageta M, Williams YN, Ghosh HP, Murakami Y. TSLC(tumor suppressor in lung cancer)1 suppresses epithelial cell scattering and tubulogenesis. *J Biol Chem*, 280: 42164-42171, 2005.
80. Sussan TE, Pletcher MT, Murakami Y, Reever RH. Tumor suppressor in lung cancer 1 (TSLC1) alters tumorigenic growth properties and gene expression. *Mol Cancer*, 4: 28, 2005.
81. Murakami Y. Involvement of a cell adhesion molecule, TSLC1/IGSF4, in human oncogenesis. *Cancer Sci*, 96: 543-552, 2005.
82. Goto A, Niki T, Chi-pin L, Matsubara D, Murakami Y, Funata N, Fukayama M. Loss of TSLC expression in lung adenocarcinoma: relationships with histological subtypes, gender, and prognostic significance. *Cancer Sci*, 96: 480-486, 2005.
83. Kikuchi S, Yamada D, Fukami T, Masuda M, Sakurai-Yageta M, Williams YN, Maruyama T, Asamura H, Matsuno Y, Onizuka M, Murakami Y. Promoter methylation of the DAL-1/4.1B predicts poor prognosis in non-small cell lung cancer. *Clin Cancer Res*, 11: 2954-2961, 2005.
84. Lung HL, Kwok A, Cheung L, Xie D, Cheng Y, Murakami M, Guan XY, Sham JS, Chua D, Protopopov AI, Zabarovsky ER, Tsao SW, Stanbridge EJ, Lung ML. TSLC1 is a tumor suppressor gene associated with metastasis in nasopharyngeal carcinoma. *Cancer Res*, 66: 9385-9392, 2006.
85. Yamada D, Yoshida M, Williams YN, Fukami T, Kikuchi S, Masuda M, Maruyama M, Ohta T, Nakae D, Maekawa A, Kitamura T, Murakami Y. Disruption of spermatogenic cell adhesion and male infertility in mice lacking TSLC1/IGSF4, an immunoglobulin superfamily cell adhesion molecule. *Mol Cell Biol*, 26: 3610-3624, 2006.

86. Weyden LVD, Arends MJ, Chausiaux OE, Lange UC, Surani MA, Affara N, Murakami Y, Adams DJ, Bradley A. Loss of TSLC1 causes male infertility due to a defect at the spermatid stage of spermatogenesis. *Mol Cell Biol*, 26: 3595–3609, 2006.
87. Kikuchi S, Yamada D, Fukami T, Maruyama T, Ito A, Asamura H, Matsuno, Y, Onizuka M, Murakami Y. Hypermethylation of the TSLC1/IGSF4 promoter is associated with tobacco smoking and a poor prognosis in primary non-small cell lung cancer. *Cancer*, 106: 1751–1758, 2006.
88. Williams YN, Masuda M, Sakurai-Yageta M, Maruyama T, Shibuya M, Murakami Y. Cell adhesion and prostate tumor suppressor activity of TSLL2/IGSF4C, an immunoglobulin superfamily molecule homologous to TSLC1/IGSF4. *Oncogene*, 25: 1446–1453, 2006.
89. Yamada D, Kikuchi S, Williams YN, Sakurai-Yageta M, Masuda M, Maruyama T, Tomita K, Gutmann DH, Kakizoe T, Kitamura T, Kanai Y, Murakami Y. Promoter hypermethylation of the potential tumor suppressor DAL-1/4.1B gene in renal clear cell carcinoma. *Int J Cancer*, 118: 916–923, 2006.
90. Furuta J, Umebayashi Y, Miyamoto K, Kikuchi K, Otsuka F, Sugimura T, Ushijima T. Promoter methylation profiling of 30 genes in human malignant melanoma. *Cancer Sci*, 95: 962–968, 2004.
91. Hagihara A, Miyamoto K, Furuta J, Hiraoaka N, Wakazono K, Seki S, Fukushima S, Tsao MS, Sugimura T, Ushijima T. Identification of 27 5' CpG islands aberrantly methylated and 13 genes silenced in human pancreatic cancers. *Oncogene*, 23: 8705–8710, 2004.
92. Kaneda A, Wakazono K, Tsukamoto T, Watanabe N, Yagi Y, Tatematsu M, Kaminishi M, Sugimura T, Ushijima T. Lysyl oxidase is a tumor suppressor gene inactivated by methylation and loss of heterozygosity in human gastric cancers. *Cancer Res*, 64: 6410–6415, 2004.
93. Okochi-Takada E, Ichimura S, Kaneda A, Sugimura T, Ushijima T. Establishment of a detection system for demethylating agents using an endogenous promoter CpG island. *Mutat Res*, 568: 187–194, 2004.
94. Takada T, Yagi Y, Maekita T, Imura M, Nakagawa S, Tsao SW, Miyamoto K, Yoshino O, Yasugi T, Taketani Y, Ushijima T. Methylation-associated silencing of the Wnt antagonist SFRP1 gene in

- human ovarian cancers. *Cancer Sci*, 95: 741-744, 2004.
95. Abe M, Ohira M, Kaneda A, Yagi Y, Yamamoto S, Kitano Y, Takato T, Nakagawara A. Ushijima T. CpG island methylator phenotype is a strong determinant of poor prognosis in neuroblastomas. *Cancer Res*, 65: 828-834, 2005.
96. Miyamoto K, Ushijima T. Diagnostic and therapeutic applications of epigenetics. *Jpn J Clin Oncol*, 35: 293-301, 2005.
97. Miyamoto K, Fukutomi T, Akashi-Tanaka S, Hasegawa T, Asahara T, Sugimura T, Ushijima T. Identification of 20 genes aberrantly methylated in human breast cancers. *Int J Cancer*, 116: 407-414, 2005.
98. Ushijima T. Detection and interpretation of altered methylation patterns in cancer cells. *Nat Rev Cancer*, 5: 223-231, 2005.
99. Ushijima T, Watanabe N, Shimizu K, Miyamoto K, Sugimura T, Kaneda A. Decreased fidelity in replicating CpG methylation patterns in cancer cells. *Cancer Res*, 65: 11-17, 2005.
100. Ushijima T, Okochi-Takada E. Aberrant methylations in cancer cells: Where do they come from? *Cancer Sci*, 96: 206-211, 2005.
101. Furuta J, Nobeyama Y, Umebayashi Y, Otsuka F, Kikuchi K, Ushijima T. Silencing of Peroxiredoxin 2 and aberrant methylation of 33 CpG islands in putative promoter regions in human malignant melanomas. *Cancer Res*, 66: 6080-6086, 2006.
102. Imura M, Yamashita S, Cai LY, Furuta JI, Wakabayashi M, Yasugi T, Ushijima T. Methylation and expression analysis of 15 genes and three normally-methylated genes in 13 ovarian cancer cell lines. *Cancer Lett*, 241: 213-220, 2006.
103. Okochi-Takada E, Nakazawa K, Wakabayashi M, Mori A, Ichimura S, Yasugi T, Ushijima T. Silencing of the UCHL1 gene in human colorectal and ovarian cancers. *Int J Cancer*, 119: 1338-1344, 2006.
104. Hatada I, Fukasawa M, Kimura M, Morita S, Yamada K, Yoshikawa T, Yamanaka S, Endo C, Sakurada A, Sato M, Kondo T, Horii A, Ushijima T, Sasaki H. Genome-wide profiling of promoter methylation in human. *Oncogene*, 25: 3059-3064, 2006.
105. Abe M, Westermann F, Nakagawara A, Takato T, Schwab M, Ushijima T. Marked and independent prognostic

- significance of the CpG island methylator phenotype in neuroblastomas. *Cancer Lett.*, 247: 253-258, 2007.
106. Nobeyama Y, Okochi-Takada E, Furuta J, Miyagi Y, Kikuchi K, Yamamoto A, Nakanishi Y, Nakagawa H, Ushijima T. Silencing of tissue factor pathway inhibitor-2 gene in malignant melanomas. *Int J Cancer*, in press.
107. Cai L-y, Abe M, Izumi S-i, Imura M, Yasugi T, Ushijima T. Identification of PRTFDC1 silencing and aberrant promoter methylation of GPR150, ITGA8 and HOXD11 in ovarian cancers. *Life Sci*, in press.
108. Etoh T, Kanai Y, Ushijima S, Nakagawa T, Nakanishi Y, Sasako M, Kitano S, Hirohashi S. Increased DNA methyltransferase 1 (DNMT1) protein expression correlates significantly with poorer tumor differentiation and frequent DNA hypermethylation of multiple CpG islands in gastric cancers. *Am J Pathol*, 164: 689-699, 2004.
109. Kanai Y, Saito Y, Ushijima S, Hirohashi S. Alterations in gene expression associated with the overexpression of a splice variant of DNA methyltransferase 3b, DNMT3b4, during human hepatocarcinogenesis. *J Cancer Res Clin Oncol*, 130: 636-644, 2004.
110. Nakagawa T, Kanai Y, Ushijima S, Kitamura T, Kakizoe T, Hirohashi S. DNA hypomethylation on pericentromeric satellite regions significantly correlates with loss of heterozygosity on chromosome 9 in urothelial carcinomas. *J Urol*, 173: 243-246, 2005.
111. Nakagawa T, Kanai Y, Ushijima S, Kitamura T, Kakizoe T, Hirohashi S. DNA hypermethylation on multiple CpG islands associated with increased DNA methyltransferase DNMT1 protein expression during multistage urothelial carcinogenesis. *J Urol*, 173: 1767-1771, 2005.
112. Peng DF, Kanai Y, Sawada M, Ushijima S, Hiraoka N, Kosuge T, Hirohashi S. Increased DNA methyltransferase 1 (DNMT1) protein expression in precancerous conditions and ductal carcinomas of the pancreas. *Cancer Sci*, 96: 403-408, 2005.
113. Chihara Y, Sugano K, Kobayashi A, Kanai Y, Yamamoto H, Nakazono A, Fujimoto H, Kakizoe T, Fujimoto K, Hirohashi S, Hirao Y. Loss of blood group A antigen expression in bladder cancer caused by allelic loss and/or methylation of the ABO

- gene. *Lab Invest*, 85: 895–907, 2005.
114. Arai E, Kanai Y, Ushijima S, Fujimoto H, Mukai K, Hirohashi S. Regional DNA hypermethylation and DNA methyltransferase (DNMT) 1 protein overexpression in both renal tumors and corresponding nontumorous renal tissues. *Int J Cancer*, 119: 288–296, 2006.
115. Peng DF, Kanai Y, Sawada M, Ushijima S, Hiraoka N, Kitazawa S, Hirohashi S. DNA methylation of multiple tumor-related genes in association with overexpression of DNA methyltransferase 1 (DNMT1) during multistage carcinogenesis of the pancreas. *Carcinogenesis*, 27: 1160–1168, 2006.
116. Sawada M, Kanai Y, Arai E, Ushijima S, Ojima H, Hirohashi S. Increased expression of DNA methyltransferase 1 (DNMT1) protein in uterine cervix squamous cell carcinoma and its precursor lesion. *Cancer Lett*, in press, 2006.
117. Noshio K, Yamamoto H, Taniguchi H, Adachi Y, Yoshida Y, Arimura Y, Endo T, Hinoda Y, Imai K. Interplay of IGF-II, IGF-I, IGF-I receptor, COX-2, and MMP-7 plays key roles in the early stage of colorectal carcinogenesis. *Clin Cancer Res*, 10: 7950–7957, 2004.
118. Yamamoto H, Horiuchi S, Adachi Y, Taniguchi H, Noshio K, Min Y, Imai K. Expression of ets-related transcriptional factor E1AF is associated with tumor progression and overexpression of matrilysin in human gastric cancer. *Carcinogenesis*, 25: 325–332, 2004.
119. Yamamoto H, Vinitketkumnuen A, Adachi Y, Taniguchi H, Hirata T, Miyamoto M, Noshio K, Imsumran A, Fujita M, Hosokawa M, Hinoda Y, Imai K. Association of matrilysin-2 (MMP-26) expression with tumor progression and activation of MMP-9 in esophageal squamous cell carcinoma. *Carcinogenesis*, 25: 2353–2360, 2004.
120. Akino K, Toyota M, Suzuki H, Mita H, Sasaki Y, Ohe-Toyota M, Issa JP, Hinoda Y, Imai K, Tokino T. The Ras effector RASSF2 is a novel tumor-suppressor gene in human colorectal cancer. *Gastroenterology*, 129: 156–169, 2005.
121. Taniguchi H, Yamamoto H, Hirata T, Miyamoto M, Oki M, Noshio K, Imsumran A, Adachi Y, Endo T, Imai K, Shinomura Y. Frequent epigenetic inactivation of Wnt inhibitory factor-1 in human gastrointestinal

- cancers. *Oncogene*, 24: 7946-7952, 2005.
122. Min Y, Adachi Y, Yamamoto H, Imsumran A, Arimura Y, Endo T, Hinoda Y, Lee C-T, Nadaf S, Carbone DP, Imai K. Insulin-like growth factor-I receptor blockade enhances chemotherapy and radiation responses and inhibits tumour growth in human gastric cancer xenografts. *Gut*, 54: 591-600, 2005.
123. Kurokawa S, Arimura Y, Yamamoto H, Adachi Y, Endo T, Sato T, Suga T, Shinomura Y, Imai K. Tumor matrilysin expression predicts metastatic potential of stage I (pT1) colon and rectal cancers. *Gut*, 54: 1751-1758, 2005.
124. Noshio K, Yoshida M, Yamamoto H, Taniguchi H, Adachi Y, Hinoda Y, Imai K. Association of Ets-related transcriptional factor ElAF expression with overexpression of matrix metalloproteinases, COX-2 and iNOS in the early stage of colorectal carcinogenesis. *Carcinogenesis*, 26: 892-899, 2005.
125. Noshio K, Yamamoto H, Adachi Y, Endo T, Hinoda Y, Imai K. Gene expression profiling of colorectal adenomas and early invasive carcinomas by cDNA array analysis. *Br J Cancer*, 92: 1193-1200, 2005.
126. Murai M, Toyota M, Suzuki H, Satoh A, Sasaki Y, Akino K, Ueno M, Takahashi F, Kusano M, Mita H, Yanagihara K, Endo T, Hinoda Y, Tokino T, Imai K. Aberrant methylation and silencing of the BNIP3 gene in colorectal and gastric cancer. *Clin Cancer Res*, 11: 1021-1027, 2005.
127. Noshio K, Yamamoto H, Mikami M, Taniguchi H, Takahashi T, Adachi Y, Imamura A, Imai K, Shinomura Y. Overexpression of poly(ADP-ribose) polymerase-1 (PARP-1) in the early stage of colorectal carcinogenesis. *Eur J Cancer*, 42: 2374-2381, 2006.
128. Kusano M, Toyota M, Suzuki H, Akino K, Aoki F, Fujita M, Hosokawa M, Shinomura Y, Imai K, Tokino T. Genetic, epigenetic, and clinicopathologic features of gastric carcinomas with the CpG island methylator phenotype and an association with Epstein-Barr virus. *Cancer*, 106: 1467-1479, 2006.
129. Kobayashi T, Sasaki Y, Oshima Y, Yamamoto H, Mita H, Suzuki H, Toyota M, Tokino T, Itoh F, Imai K, Shinomura Y. Activation of the ribosomal protein L13 gene in human gastrointestinal cancer. *Int J Mol Med*, 18: 161-170, 2006.
130. Akino K, Toyota M, Suzuki H, Imai T,

- Maruyama R, Kusano M, Nishikawa N, Watanabe Y, Sasaki Y, Abe T, Yamamoto E, Tarasawa I, Sonoda T, Mori M, Imai K, Shinomura Y, Tokino T. Identification of DFNA5 as a target of epigenetic inactivation in gastric cancer. *Cancer Sci*, 2006 Nov 3; [Epub ahead of print].
131. Mikami M, Noshio K, Yamamoto H, Takahashi T, Maehata T, Taniguchi H, Adachi Y, Imamura A, Fujita M, Itoh F, Imai K, Shinomura Y. Mutational analysis of  $\beta$ -catenin and the RAS-RAF signaling pathway in early flat-type colorectal tumours. *Eur J Cancer*, 42: 3065-3072, 2006.
132. Noshio K, Yamamoto H, Takahashi T, Mikami M, Taniguchi H, Miyamoto N, Adachi Y, Arimura Y, Itoh F, Imai K, Shinomura Y. Genetic and epigenetic profiling in early colorectal tumors and prediction of metastatic potential in pT1 (early invasive) colorectal cancers. *Carcinogenesis*, in press, 2006 Dec 20; [Epub ahead of print].
133. Imsumran A, Adachi Y, Yamamoto H, Li R, Wang Y, Min Y, Piao W, Noshio K, Arimura Y, Shinomura Y, Hosokawa M, Lee CT, Carbone DP, Imai K. Insulin-like growth factor-I receptor as a marker for prognosis and a therapeutic target in human esophageal squamous cell carcinoma. *Carcinogenesis*, in press, 2006 Dec 20; [Epub ahead of print].
134. Hirata T, Yamamoto H, Taniguchi H, Horiuchi S, Oki M, Adachi Y, Imai K, Shinomura Y. Characterization of immune escape phenotype of human gastric cancers with and those without high-frequency microsatellite instability. *J Pathol*, 211: 516-523, 2007.
135. Takahashi T, Noshio K, Yamamoto H, Mikami M, Taniguchi H, Miyamoto N, Adachi Y, Itoh F, Imai K, Shinomura Y. Flat-type colorectal advanced adenomas (laterally spreading tumors) have different genetic and epigenetic alterations from protruded-type advanced adenomas. *Mod Pathol*, 20: 139-147, 2007.
136. Miyamoto N, Yamamoto H, Taniguchi H, Miyamoto C, Oki M, Adachi Y, Imai K, Shinomura Y. Differential expression of angiogenesis-related genes in human gastric cancers with and those without high-frequency microsatellite instability. *Cancer Lett*, in press.
- H. 知的財産権の出願・登録状況  
(予定を含む)
1. 特許取得
    - 1) PCT/JP2004/001574 「薬剤耐性を獲得し

- たがん細胞の検出方法」2004. 2. 4、出願番号：特願 2004-36028、PCT/JP2004/001574、PBM95PCT
- 2) PTC/JP2004/002294「新規キメラ蛋白質およびこれをコードする遺伝子、並びに、これらの遺伝子と蛋白質を用いた白血病の判別手段」2004. 2. 2、出願番号：PTC/JP2004/002294、PBM96PCT
- 3) 特願 2004-81926 「ゲノムDNAの定着基盤と当該基盤を用いた染色体異常並びにそれに起因する疾患の検出方法」2004. 3. 22、出願番号：特願 2004-81926
- 4) 特願 2004-84795 「食道がんの検出方法、および、抗食道がん物質のスクリーニング方法」2004. 3. 23、出願番号：特願 2004-81926
- 5) 特願 2004-88424 「特定のがん関連遺伝子を用いるがんの検出方法及びがんの抑制方法」2004. 3. 25.
- 6) 特願 2005-309921 「がん抑制剤」2005. 10. 25.
- 7) 特願 2006-078786 「がん抑制剤」2006. 3. 22.
- 8) 特願 2006-078787 「がんの検出方法および抑制方法」2006. 3. 22
- 9) 特願 2006-109312 「がん関連欠失遺伝子マーカーを用いたがんの診断方法」2006. 4. 12.
- 10) 特願 2006-118030 「VLDLR 遺伝子の検出による胃がんの検出方法」2006. 4. 21.
- 11) 特願 2006-204601 「がん抑制剤」2006. 7. 27
- 12) 特願 2006-255155 「多発性骨髓腫の検出方法および制御方法」2006. 9. 21.
- 13) 特願 2006-303331 「食道がんの検出方法」2006. 11. 8.
- 14) 特願 2006-342462 「がんの診断マーカーならびに治療の標的分子 OSLC1」2006. 12. 20 :
- 15) 出願：Hedgehog シグナル活性調節剤、細胞増殖調節剤及びその使用方法、坂元亨宇他 2 名、2006. 11. 24、特願 2006-317576
- 16) 出願番号：特願 2005-266127 (日本)、発明者：村上善則、増田万里、発明の名称：がんの診断、処置および／または予防、および／または浸潤・転移の抑制のための方法、システムおよび組成物ならびに関連するスクリーニング方法、出願人：財団法人ヒューマンサイエンス振興財団、出願日：2005 年 9 月 13 日、国際特許分類：A61K、国内優先権出願、出願日：2006 年 9 月 13 日、出願番号：2006-248753
- 17) 出願番号：特願 2005-380332、発明者：村上善則、発明の名称：小細胞肺がんの診断のための方法、システムおよび組成物ならびに関連するスクリーニング方法、出願人：国立がんセンター、出願日：2005 年 12 月 28 日、PCT 出願、発明の名称：小細胞肺がんの診断のための方法、システムおよび組成物ならびに関連するスクリーニング方法、優先日：2005/12/28 (2005-380332)、PCT 出願：PCT/JP2006/325937 号 (2006/12/26 出願)、国内移行期限：2008/06/28、伺い予定：2008/02/28、指定国：全、法域：PCT、日本指定の取り下げ予定：なし、出願人：国

立がんセンター総長、発明者：村上善則優  
先権主張：2005/12/12 \*JP2005-380332

2. 實用新案登録 該当なし  
3. その他 該当なし

研究成果の刊行に関する一覧表

書籍

| 著者氏名                           | 論文タイトル名   | 書籍全体の<br>編集者名 | 書籍名   | 出版社名     | 出版地     | 出版年  | ページ     |
|--------------------------------|---|---------------|---|----------|---------|------|---------|
| Kanai Y,<br>Arai E,<br>Etoh T. | Role of<br>immunohistochemic<br>al expression of<br>DNA<br>methyltransferase<br>1 protein in<br>gastric<br>carcinoma. | Hayat, MA     | Handbook of<br>Immunohisto-<br>chemistry and<br><i>in situ</i><br>Hybridization<br>of Human<br>Carcinomas.<br>Vol. 4:<br>Molecular<br>Genetics,<br>Gastro-<br>intestinal<br>Carcinoma,<br>and Ovarian<br>Carcinoma, | Elsevier | CA, USA | 2006 | 257-261 |
|                                |   |               |   |          |         |      |         |
|                                |   |               |   |          |         |      |         |

雑誌

| 発表者氏名  | 論文タイトル名  | 発表誌名              | 巻号  | ページ       | 出版年  |
|--|--|-------------------|-----|-----------|------|
| Yamada Y, Itano N, Narimatsu H, Kudo T, Morozumi K, <u>Hirohashi S</u> , Ochiai A, Ueda M, Kimata K. | Elevated transcript level of hyaluronan synthasel gene correlates with poor prognosis of human colon cancer. | Clin Exp Metastas | 21  | 57-63     | 2004 |
| Shibata T, Kokubu A, Sekine S, <u>Kanai Y</u> , <u>Hirohashi S</u> .                                 | Cytoplasmic p120ctn regulates the invasive phenotypes of E-cadherin-deficient breast cancer.                 | Am J Pathol       | 164 | 2269-2278 | 2004 |
| Honda K, Yamada T, Seike M, Hayashida Y, Idogawa M, Kondo T, Ino Y, <u>Hirohashi S</u> .             | Alternative splice variant of actinin-4 in small cell lung cancer.   | Oncogene          | 23  | 5257-5262 | 2004 |

|   |   |            |    |           |      |
|---|---|------------|----|-----------|------|
| Yanagihara K,<br>Tanaka H,<br>Takigahira M,<br>Ino Y, Yamaguchi<br>Y, Toge T,<br>Sugano K,<br><u>Hirohashi S.</u>   | Establishment of two<br>cell lines from human<br>gastric scirrhous<br>carcinoma that<br>possess the potential<br>to metastasize<br>spontaneously in nude<br>mice.                 | Cancer Sci | 95 | 575-582   | 2004 |
| Akimoto S,<br>Nakanishi Y,<br><u>Sakamoto M,</u><br><u>Kanai Y,</u><br><u>Hirohashi S.</u><br>Laminin 5 $\beta$ 3 and<br>$\gamma$ 2 chains are<br>frequently<br>coexpressed in<br>cancer cells. | Laminin 5 $\beta$ 3 and $\gamma$ 2<br>chains are frequently<br>coexpressed in cancer<br>cells.  | Pathol Int | 54 | 688-692   | 2004 |
| Yokoo H, Kondo<br>T, Fujii K,<br>Yamada T, Todo<br>S, <u>Hirohashi S.</u>   | Proteomic signature<br>corresponding to<br>alpha fetoprotein<br>expression in liver<br>cancer cells.  | Hepatology | 40 | 609-617   | 2004 |
| Seike M, Kondo<br>T, Fujii K,<br>Yamada T, Gemma<br>A, Kudoh S,<br><u>Hirohashi S.</u>  | Proteomic signature<br>of human cancer<br>cells.  | Proteomics | 4  | 2776-2788 | 2004 |
| Loukopoulos P,<br>Kanetaka K,<br>Takamura M,<br>Shibata T,<br><u>Sakamoto M,</u><br><u>Hirohashi S.</u>   | Orthotopic<br>transplantation<br>models of pancreatic<br>adenocarcinoma<br>derived from cell<br>lines and primary<br>tumors and displaying<br>varying metastatic<br>activity.     | Pancreas   | 29 | 193-203   | 2004 |
| Shimamura T,<br>Yasuda J, Ino Y,<br>Gotoh M,<br>Tsuchiya A,<br>Nakajima A,<br><u>Sakamoto M,</u><br><u>Kanai Y,</u><br><u>Hirohashi S.</u>  | Dysadherin expression<br>facilitates cell<br>motility and<br>metastatic potential<br>of human pancreatic<br>cancer cells.   | Cancer Res | 64 | 6989-6995 | 2004 |
| Sekine S,<br>Shimoda T,<br>Nimura S,<br>Nakanishi Y,<br>Akasu T, Katai<br>H, Gotoda T,<br>Shibata T,<br><u>Sakamoto M,</u><br><u>Hirohashi S.</u>   | High-grade dysplasia<br>associated with<br>fundic gland<br>polyposis in a<br>familial adenomatous<br>polyposis patient,<br>with special<br>reference to APC<br>mutation profiles. | Mod Pathol | 17 | 1421-1426 | 2004 |

|   |  |                                    |     |           |      |
|---|--|------------------------------------|-----|-----------|------|
| Sekine S, Takata T, Shibata T, Mori M, Morishita Y, Noguchi M, Uchida T, <u>Kanai Y</u> , <u>Hirohashi S.</u>       | Expression of enamel proteins and LEF1 in adamantinomatous craniopharyngioma: evidence for its odontogenic epithelial differentiation.   | Histo-pathology                    | 45  | 573-579   | 2004 |
| Nakanishi Y, Akimoto S, Sato Y, <u>Kanai Y</u> , <u>Sakamoto M</u> , <u>Hirohashi S.</u>                            | Prognostic significance of dysadherin expression in tongue cancer: immunohistochemical analysis of 91 cases.   | Appl Immunohisto- chem Mol Morphol | 12  | 323-328   | 2004 |
| Sanada T, Yokoi S, Arii S, Yasui K, Imoto I, <u>Inazawa J.</u>  | Skp2 overexpression is a p27kip1-independent poor prognosticator in patients with biliary tract cancers.   | Cancer Sci                         | 95  | 969-976   | 2004 |
| Tanami H, Imoto I, Hirasawa A, Yuki Y, Sonoda I, Inoue J, Yasui K, Misawa-Furihata A, Kawakami Y, <u>Inazawa J.</u> | Involvement of overexpressed wild-type BRAF in the growth of malignant melanoma cell lines.  | Oncogene                           | 23  | 8796-8804 | 2004 |
| Misawa A, Hosoi H, Imoto I, Iehara T, Sugimoto T, <u>Inazawa J.</u>   | Translocation (1;22) (p36;q11.2) with concurrent del(22) (q11.2) resulted in homozygous deletion of SNF5/INI1 in a newly established cell line derived from extrarenal rhabdoid tumor. | J Hum Genet                        | 49  | 586-589   | 2004 |
| <u>Inazawa J</u> , Inoue J, Imoto I.  | Comparative genomic hybridization (CGH) arrays pave the way for identification of novel cancer-related genes.  | Cancer Sci                         | 95  | 559-563   | 2004 |
| Yokoi S, Yasui K, Mori M, Iizasa T, Fujisawa T, <u>Inazawa J.</u>   | Amplification and overexpression of SKP2 are associated with metastasis of non-small-cell lung cancers to lymph nodes.   | Am J Pathol                        | 165 | 175-180   | 2004 |
| Inoue J, Otsuki T, Hirasawa A, Imoto I, Matsuo Y, Shimizu S, Taniwaki M, <u>Inazawa J.</u>                          | Overexpression of PDZK1 within the 1q12-q22 amplicon is likely to be associated with drug-resistance phenotype in multiple myeloma.  | Am J Pathol                        | 165 | 71-81     | 2004 |

|   |  |            |    |           |      |
|---|--|------------|----|-----------|------|
| Yuki Y, Imoto I, Imaizumi M, Hibi S, Kaneko Y, Amagasa T, Inazawa J.  | Identification of a novel fusion gene in a pre-B acute lymphoblastic leukemia with t(1;19) (q23;p13).  | Cancer Sci | 95 | 503-507   | 2004 |
| Sonoda I, Imoto I, Inoue J, Shibata T, Shimada Y, Chin K, Imamura M, Amagasa T, Gray JW, Hirohashi S, Inazawa J.            | Frequent silencing of low density lipoprotein receptor-related protein 1B (LRP1B) expression by genetic and epigenetic mechanisms in esophageal squamous-cell carcinoma.                         | Cancer Res | 64 | 3741-3747 | 2004 |
| Yasui K, Mihara S, Zhao C, Okamoto H, Saito-Ohara F, Tomida A, Funato T, Yokomizo A, Naito S, Imoto I, Tsuruo T, Inazawa J. | Alteration in copy numbers of genes as a mechanism for acquired drug resistance.   | Cancer Res | 64 | 1403-1410 | 2004 |
| Wenlin Du, Hattori Y, Hashiguchi A, Kondoh K, Hozumi N, Ikeda Y, Sakamoto M, Hata J, Yamada T.                              | Tumor angiogenesis in the bone marrow of multiple myeloma patients and its alteration by thalidomide treatment.  | Pathol Int | 54 | 285-294   | 2004 |
| Chuma M, Saeki N, Yamamoto Y, Ohta T, Asaka M, Hirohashi S, Sakamoto M.   | Expression profiling in hepatocellular carcinoma with intrahepatic metastasis: identification of high-mobility group I (Y) protein as a molecular marker of hepatocellular carcinoma metastasis. | Keio J Med | 53 | 90-97     | 2004 |
| Chuma M, Sakamoto M, Yasuda J, Fujii G, Nakanishi K, Tsuchiya A, Ohta T, Asaka M, Hirohashi S.                              | Overexpression of cortactin is involved in motility and metastasis of hepatocellular carcinoma.  | J Hepatol  | 41 | 629-636   | 2004 |

|  |   |                          |     |           |      |
|--|---|--------------------------|-----|-----------|------|
| Takamura M,<br>Ichida T,<br>Matsuda Y,<br>Kobayashi M,<br>Yamagiwa S,<br>Genda T, Shioji<br>K, Hashimoto S,<br>Nomoto M,<br>Hatakeyama K,<br>Ajioka Y,<br><u>Sakamoto M</u> ,<br><u>Hirohashi S</u> ,<br>Aoyagi Y. | Reduced expression of liver-intestine cadherin is associated with progression and lymph node metastasis of human colorectal carcinoma.  | Cancer Lett              | 212 | 253-259   | 2004 |
| Surace EI,<br><u>Murakami Y</u> ,<br>Scheithauer BW,<br>Perry A, Gutmann<br>DH.  | Tumor Suppressor in Lung Cancer-1 (TSLC1) expression is lost in sporadic meningioma.  | J Neuropathol Exp Neurol | 63  | 1015-1027 | 2004 |
| Lung HL, Cheng<br>Y, Kumaran MK,<br>Liu E. TB,<br><u>Murakami Y</u> , Chan<br>CY, Yau WL,<br>Stanbridge EJ,<br>Lung ML.  | Fine mapping of 11q22-23 tumor suppressive region and involvement of TSLC1 in nasopharyngeal carcinoma.   | Int J Cancer             | 112 | 628-635   | 2004 |
| Saino M,<br>Maruyama T,<br>Sekiya T, Kayama<br>T, <u>Murakami Y</u> .  | Inhibition of angiogenesis in human glioma cell lines by antisense RNA from the soluble guanylate cyclase genes, GUCY1A3 and GUCY1B3.   | Oncol Rep                | 12  | 7-52      | 2004 |
| <u>Murakami Y</u> ,<br>Isogai K, Tomita<br>H, Sakurai-Yageta M,<br>Maruyama T,<br>Hidaka A, Nose<br>K, Sugano K,<br>Kaneko A.  | Detection of allelic imbalance in the gene expression of hMSH2 or RB1 in lymphocytes from pedigrees of hereditary non-polyposis colorectal cancer and retinoblastoma by an RNA difference plot. | J Hum Genet              | 49  | 635-641   | 2004 |