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Division of Clinical and Experimental Oncology Department of Translational Cancer Research

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The area of interest of this department is the molecular and genetic information research through every possible organism in human cells. Especially our attention is focused on the genomic background of disease such as cancer and developmental research for the new treatment based on the information. Recent efforts are directed mainly toward understanding the molecular mechanisms of drug resistance in cancer cells, apoptosis, and cell aging, developing new anticancer treatments, molecular target therapy and personalized medicine. We have surveyed DNA and RNA variations using a variety of technologies such as cDNA microarray, and attempted to develop a new cancer therapy, tailored chemotherapy which is based on the acquaintance that an individual's genomic make-up links to their response to drugs, and discover a new molecular target for drug development.

The research projects have been carried out and/or are being planned from various aspects during the academic year of 2002 as follows:

1. Development research for personalized medicine
   a) For cancer
   b) For other multi-factorial diseases
2. Genomics-based drug discovery and molecular target therapy for chemotherapy-resistant solid tumors
3. Regulation mechanisms of telomerase in cancerous and non-cancerous cells
4. Cellular response to hypoxia in cancers and functional roles of HIF-1α in the mechanisms
5. Transcriptional regulation of dihydropyrimidine dehydrogenase gene (*DPYD*) and its disorder
   a) Molecular mechanisms of the transcriptional regulation
   b) Aberrant hypermethylation of *DPYD* and its effect on cellular response to 5-fluorouracil (5-FU)
6. Molecular biology of aging

7．Rejuvenating research

Those researches were supported by several grants as follows: The Science Promotion Fund of the Ministry of Education, Culture, Science, Sports and Technology of Japan, 1） Grant-in Aid for Scientific Research（B）(2)(No.14370390） Tailored neo-adjuvant chemotherapy for gastrointestinal cancers based on the comprehensive expression analysis using cDNA microarray（delegate: M. Nishiyama）, 2）Grant-in Aid for Scientific Research（A）(2)(No.13307050): Comprehensive analysis on the biology of neuroblastoma using microarray technique: for the establishment of individualized therapy.（collaborator: K. Hiyama）, 3)Grant-in Aid for Scientific Research（B）(2)(No.13557051): Development of novel KL-6-associated serum markers using high sensitive Electro Chemiluminscent Immunoassay.（collaborator: K. Hiyama）, 4）Grant-in Aid for Scientific Research（B）（2）（No.14380261): Study of genetic effects of A-bomb radiation using microarray CGH.（collaborator: K. Hiyama）, 5）Grant-in Aid for Scientific Research（B）(2)(No.14370197): Study on the potential of KL-6 as a disease-modifying or a prognostic factor of idiopathic interstitial pneumonia.（collaborator: K. Hiyama）, 6）Grand-in Aid for Scientific Research on Priority Areas（2)(No.14028043): Transgenic mice of active forms of hypoxia-inducible factor-1α.（delegate: K. Tanimoto）, 7）Grand-in-Aid for Scientific Research（C)(2)(No.13672099): Molecular diagnosis and therapy based on mechanisms of the regulation of hypoxia-inducible factor-1α.（collaborator: K. Tanimoto）, 8）Gran-in-Aid for Development of Highly Advanced Medical Technology（B)(No.K-500): Clinical application of telomere and telomerase as targets for molecular diagnosis of malignant solid tumors and prognosis（collaborator: K. Hiyama）, 9）Grant-in-Aid for University and Industry Collaboration（A): Development of practical gene analysis system for tailored chemotherapy for gastric cancer and its clinical application.（delegate: M. Nishiyama）. 10)Entrusted Grant from Division of Applied Oncology of Taiho Pharm. Co. Ltd: Transcriptional regulation of dihydropyrimidine dehydrogenase gene（*DPYD*）.（delegate: M. Nishiyama）

With respect to personal affairs, Dr. K. Hiyama has joined us as associate professor since Jan. 1/ 2003, and Dr. T. Noguchi has started his research with us since Apr. 1/2002. Lecturer T. Kumazaki will move to Suzugamine Women's college as a professor on Apr. 1/2003. Dr. T. Satoh learned several experimental techniques in our laboratory from Apr.1/ 2002 to Sep. 1/2002 as post-graduate student fellow. Dr. M. Sasaki was awarded the degree of Doctor for medical science（Ph.D.）.

We had a total of 11 presentations at symposium, invited, educational and special lectures in this year. Prof. M. Nishiyama was appointed as members of "Council, Educational Committee for Clinical Oncologist, and Editorial Committee of the Japan Society of Clinical Oncology", "Council of Japanese Society of Medical Oncology", "Council of the Japanese Gastric Cancer Society", "Board of Secretary of Japanese Society of Molecular Target Therapy", "Board of Secretary of Japanese Society of Strategies for Cancer Research and Therapy", "Board of Secretary of Research Society for Sensitivity of Cancer", "Council of Hiroshima Cancer therapy Society", "Academic advisor of National Institute of Science and Technology Policy, the Ministry of Education, Culture, Science, Sports and Technology of Japan", "Council and Committee for Clinical Trials of Japanese Foundation for Multidisciplinary Treatment of Cancer", "Council and Academic Committee of Japan Clinical Cancer Research Organization", and "Organizing Committee of the Tokyo Forum of New Anticancer drugs". Assoc. Prof. K. Hiyama was appointed as members of "Council of Japanese Society of Internal Medicine, Chugoku District", "Council of Japanese Respiratory Society, Chugoku-Sikoku District", "Council of Japan Lung Cancer Society, Chugoku-Sikoku District", "Academic Adviser: Japanese Society of Molecular Target for Gynecological Cancer", "Expert Adviser（Genetic Counselor): Radiation Effects Research Foundation", and "Board of Society of Okunojima Poison Gas Casualty".

1．Development research for personalized medicine

a)For cancer

Tanaka. T., Satoh T., Kaneyasu, K., Noguchi, T., Tanimoto, K., Nishiyama, M.

Purpose: Some anticancer drugs work better in some patients than in others, and some drugs may even be highly toxic to certain patients. Pharmacogenomics is about spotting correlation such responses to drugs and the genetic profiles of patients. We attempt to develop a new anticancer chemotherapy system to choice the best anticancer chemotherapy based on the

prediction of individual's response to drug by gene expression and mutational analysis.

Methods and Results: Pilot clinical trial of our first model, in which the most active chemotherapy is selected for gastric cancer patients according to their gene expression profiles of 18 drug resistance factors, is continued to evaluate the clinical utility. Further, we have started a pharmacogenomic study combined with phase I/II clinical evaluation of paclitaxel weekly administration for metastatic gastric cancer and irinotecan (CPT-11) single administration for colo-rectal cancers as adjuvant setting. Activity of anticancer chemotherapy is determined by intricate interplay of multiple genes related to anticancer effect and toxicity. Using cDNA microarray, we also attempt to identify the most important participants among huge number of human genes including functionally unknown ones and clarify the complicated functional network. In cDNA microarray analysis, interpretation of the huge expression-signals or -profiles into biology is a very serious problem, and we developed novel data analysis methods for normalization of the expression signal and for identifying the most important genes. Additionally, to understand the multi-dimensional interaction of genes, we have analyzed the expression data by simplified sliced inverse regression (SSIR) method and developed a new prospective model for individualizing drug therapy. We are planning a new cooperative study with Dr. Hayashizaki, Genome Sci. Lab., Inst. Phys. Chem. Res. (RIKEN), to develop a more active system for analysis and research using cDNA microarray. Identification of DNA variants of drug metabolic enzyme genes, such as CYP3A4, CYP2C8, and carboxylesterase, is studied also in samples from cancer patients to understand the link between individual's genetic make-up and their response to drug therapy. A cDNA microarray- and DHPLC-based predictive system of individual's response and toxicity to certain drugs will be developed.

b) For other multi-factorial diseases

Hiyama, K., Nishiyama, M.

Purpose: To establish the individualized therapy for multi-factorial diseases, we investigated the relationship between the genetic background and development of diseases or sensitivity to drugs.

Methods: 1) Genetic polymorphisms in the *EPHX1*, *CYP1A1*, *CYP2E1*, *GSTM1*, *GSTT1*, *GSTP1*, and *HMOX1* were investigated and the relationship between their genotypes and emphysematous changes of the lung was investigated. 2) Genetic polymorphisms in the *TYMS* and *MTHFR* were investigated and the relationship between their genotypes and effects or adverse effects of methotrexate (MTX) was investigated.

Results: 1) In heavy smokers, whereas no polymorphism demonstrated significant relationship between the allele frequency and emphysematous changes of the lung, combination of some genetic polymorphisms in the enzymes associated with detoxification of smoke products, i.e., combination of the *EPHX1* genotype representing putative very slow phenotype and type 1 of the *HMOX1* gene, was considered to predispose smokers to the development of emphysematous changes. 2) In patients with rheumatoid arthritis, the polymorphisms in the promoter region and the 3'UTR of the *TYMS* were associated with sensitivity to low-dose MTX therapy, while no association between the polymorphisms and MTX-related adverse effects was observed. In addition, existence of apparent ethnic variations in the distribution of their genotypes was found indicating the importance of genotyping to predict and determine the appropriate dose in the low-dose MTX therapy.

2. Genomics-based drug discovery and molecular target therapy for chemotherapy-resistant solid tumors

Sasaki, M., Noguchi, T., Hiyama, K., Nishiyama, M.

urpose: Prognoses of solid tumors such as gliomas and gastrointestinal cancers remain poor. We have attempted to discover new targets for developing new drugs and develop a new treatment system, molecular target anticancer therapy, which may achieve tumor selective kill through modulation of the target specific to tumor cells.

Methods and Results: 1) Discovery of novel drug targets: Immortal normal cells have been established by the introduction of human telomerase gene (*hTERT*). Using RIKEN human 25K array, expression of huge number of human genes is analyzed

in a various settings such as normal cells vs immortal normal cells, immortal normal cells vs cancer cells, and normal cells vs cancer cells, to pick up genes closely related to the metastatic and immortalized characteristics of cancer cells. Then, expression of candidate genes is monitored in multiple time points from multiple cancer cell lines with or without drug treatment to identify the significant genes involved in cancer metastasis and immortalization, which cannot be controlled by the previously developed drugs. We have determined approximately 30 candidate genes, of which product may be a potent target for developing new anticancer drugs. 2)Molecular target anticancer therapy: Cellular resistant factors to anticancer drug have been focused on as a molecular target for enhancing drug efficacy. Our studies have shown that the possible target to be modulated is Bcl-2 when 5-fluorouracil(5-FU)is used. We found that the suppression in the expression increased 5-FU activity significantly in cancer cells. However, such remarkable increase in 5-FU activity could not be observed in human fibroblast cells. Bcl-2 target therapy may achieve tumor selective kill.

3. Regulation mechanisms of telomerase in cancerous and non-cancerous cells

Noguchi, T., Hiyama, K., Tanimoto, K., Kumazaki, T., Nishiyama, M.

Purpose: Expression of telomerase is considered to be essential for attainment of immortality in almost all cancer cells as well as for elongation of cellular life span in normal cells. To develop new anti-cancer strategy and apply to regenerative medicine, we investigate the regulation mechanisms of telomerase.

Methods: 1)Using cDNA microarrays, expression profiles are compared between before and after telomerase induction in human fibroblasts and endothels. 2)Establishing immortal bronchial epithelial cells, expression profiles are compared between before and after telomerase induction also in human epithelial cells. 3)Telomerase activity levels are compared between the primary and metastatic lesions of solid tumors, and the relationships with the mRNA expression profiles are analyzed. 4)From 1)-3)data, regulation mechanisms in cancerous and non-cancerous cells are compared.

Results: 1)Various transcription factors and oncogene-related genes as well as unknown genes were detected to be differentially expressed before and after induction of telomerase. The representative genes are now quantitatively analyzed for confirmation. 2)Telomerase activity levels correlated with deletion of TP53 and/or RB1 in lung cancer. For cancers in digestive organs, the research project"Investigation of genes responsible for carcinogenesis and progression of cancers in digestive organs" was approved by the institutional ethics committee for genome research in this year.

4. Cellular response to hypoxia in cancers and functional roles of HIF-1α in the mechanisms

Tanimoto, K., Hiyama, K., Nishiyama, M.

Purpose and Methods: One of the key factors regulating hypoxic response is hypoxia-inducible factor-1α (HIF-1α). To evaluate genetic alterations of HIF-1α *in vivo*, genomic DNA were subjected to DHPLC and sequencing analyses. We performed also *in vitro* functional assay and molecular epidemiological analysis to estimate functional and clinical significance.

Results: We found two single-nucleotide polymorphisms (SNPs) resulting in an amino-acid substitution in the N-terminal activation domain (N-TAD)of HIF-1α (P582S: 18.2%, A588T: 7.3%). Interestingly, these variant forms of HIF-1α strongly increased transcriptional activity under both normoxic and hypoxic conditions. Furthermore, tumors from HNSCC patients with heterozygous alleles having P582S or A588T had significantly increased numbers of microvessels compared with those with homozygous WT did(P=0.02). In addition, all patients with tumors of T1 (below 2cm diameter) were homozygous WT, while 14 of 47 patients with tumors of ≥T2 were heterozygous. The elevated transactivation capacity of variant forms of HIF-1α implies a role of *HIF-1α* polymorphisms in generating individually-different tumor progression. Analysis of transgenic mice of *HIF-1α* variants is on going.

5. Transcriptional regulation of dihydropyrimidine dehydrogenase gene (*DPYD*) and its disorder

a) Molecular mechanisms of the transcriptional regulation

Ukon, K., Noguchi, T., Tanimoto, K., Nishiyama, M.

Purpose: Dihydropyrimidine dehydrogenase (DPD) is a key enzyme in the catabolic pathway of the anticancer drug 5-FU, and is expected as a prediction marker of individual response to the drug. To clarify the mechanisms of transcriptional regulation of DPD gene is hopeful not only for predictions but also for new molecular-targeting therapy by way of expression control.

Materials and Methods: The 5' flanking region of DPD gene (*DPYD*) was subcloned into pBluescript from λ phage of human placenta genome library, and its nucleotide sequence was determined. The region was fused to the luciferase reporter gene and transiently transfected into several cancer cell lines. A series of deletion mutants of the region were constructed and analyzed. Gel-shift assay was performed using several candidates for cis-element as probes.

Results: The nucleotide sequence of *DPYD* 5' flanking region contains the novel upstream region (−2918～−1153 bp) and the previously reported region (−1152～+83 bp, Diasio *et al*., 2000). The full-length promoter activity varied among cancer cell lines. Comparative analysis of deletion mutants suggested several *cis*-elements, and their function may differ among cancer cell lines. Gel-shift assay revealed DNA binding protein complex to several candidates of *cis*-element. Details are under investigation.

b) Aberrant hypermethylation of DPYD and its effect on cellular response to 5-fluorouracil (5-FU)

Noguchi, T., Tanimoto, K., Ukon, K., Hiyama, K., Nishiyama, M.

Purpose: To develop a novel prediction system of individual response to 5-FU and a new therapy to enhance 5-FU activity, we attempted to identify methylated CpG sites in the *DPYD* promoter region and clarify their roles in transcription of *DPYD*.

Methods: 1) *DPYD* expressions in several cancer cell lines were analyzed by real-time RT-PCR method. 2) Exogenous *DPYD* promoter activities were analyzed by luciferase reporter assay. 3) Genomic DNA was treated with sodium bisulfite and subjected to sequencing analysis. 4) HepG2 was treated with 5-aza-cytidine and then analyzed on the *DPYD* expression and 5-FU sensitivity by Real-time RT PCR method and MTT assay, respectively.

Result: 1) *DPYD* expression levels varied among cell lines, some of them were undetectable. 2) Luciferase reporter assay revealed HepG2 and HSC3 had relatively strong promoter activity of *DPYD* but endogenous *DPYD* was not expressed. 3) We found methylated CpG sites by bisulfite sequencing analysis. Especially, the methylation of CpG site at +8 bp correlated with low expression. 4) After 5-aza-cytidine treatment to HepG2, the *DPYD* expression was restored along with modification in the sensitivity to 5-FU.

6. Molecular biology of aging

Kumazaki, T., Sasaki, M., Nishiyama, M.

Purpose: It is well known that aging is accelerated by radiation, but its mechanism has not been resolved. To uncover the mechanism, it is a prerequisite to know the mechanism of normal aging. Because many and complex elements participate in the aging process, it is necessary to use a simpler system. Thus, we adopted cultured cells to investigate aging at the cellular level. On the other hand, many evidences have shown that not only the genetic program but also environmental stresses affect to the aging process. We have started to investigate roles of the *bcl-2* gene, which can suppress the influence of environmental stresses. In the future, we will attempt to regulate aging or life span by controlling BCL-2 function.

Methods and Results: We have shown that the BCL-2 level is decreased with cellular aging. This result suggests that senescent cells are sensitive to death induction, but it has been shown that senescent cells are resistant to death induction. This

resistant nature is derived from that growth-arrested cells (both young and senescent) are resistant to death induction. Next, we investigated the influence of down-regulation of BCL-2. We reduced the BCL-2 level by treating cells with anti-sense oligo DNA for *bcl-2* gene or by transfecting an expression plasmid of anti-sense *bcl-2* gene into cells, and cellular life span and the frequency of cell death were measured. The results showed that cells having less BCL-2 died more frequently than normal cells and cellular life span of them was shorter than normal cells. Because the death was significantly reduced by an antioxidant, it is suggested that reactive oxygen species, environmental stress factors, are the major cause of the death and BCL-2 participates in protection from the death. The more frequent death in cells with less BCL-2 leads to the shorter life span of the culture.

In this year, we investigated the effect of overexpression of *bcl-2* on cell death and life span. The culture of bcl-2-transfected normal fibroblasts showed a shorter life span by about 12 PDL compared to that of vector transfectants (64 vs. 76 PDLs, respectively). An MTT assay revealed that BCL-2-overexpressing cells (HCA2/bcl-2) showed greater growth suppression due to hydrogen peroxide or doxorubicin treatment than did vector control cells (HCA2/vector). We observed a significant number of dead cells in the HCA2/bcl-2 culture, but not in the HCA2/vector culture. Other BCL-2 family proteins with both anti-apoptotic and pro-apoptotic activity and other apoptosis-related factors were maintained at similar levels, indicating that overexpression of BCL-2 is the major reason that normal fibroblasts are sensitized to cell death. Inhibitors of caspases suppressed cell death of HCA2/bcl-2 effectively, suggesting involvement of caspase 3-, 8- and 9-dependent pathways in cell death and that the form of death is apoptosis. Unexpectedly, involvement of active MEK in cell death was shown by the use of its inhibitor, suggesting that crosstalk between BCL-2 and the MAP kinase cascade regulates death as well as life span. Further investigation for the contribution of Bcl-2 on aging or life span is now going on.

7. Rejuvenating research

Kumazaki, T., Nishiyama, M.

Purpose: It is well known that normal cells senesce. To the regenerative medicine for radiation damages, it is a major concern that cells undergo senescence or irreversible growth arrest, because a substantially large number of population doublings of patient cells in vitro is needed to cure the patient. This research intends to solve the problem by rejuvenating or immortalizing cells.

Methods and Results: There is a hypothesis that cellular life span is limited by the length of telomeres, which occur at the end of chromosomes. By introducing the telomerase gene into fibroblast cells, we succeeded to obtain a clone which did not senesce and probably had been immortalized. Nature of the cells is not different from normal fibroblasts and they have not acquired the ability to form tumors. If we use these cells to regenerate a tissue, the tissue might maintain the ability comparable to that from young donor all over the life of the recipient.

Next, we introduced the telomerase gene into normal human vascular endothelial cells, and established an immortal endothelial cell clone. We checked changes in expression of telomerase gene, telomerase activity, and telomere length during elongated proliferation. These are mostly maintained through the investigated period. To check if the clone still has normal characteristics of its parental cell, we checked nuclear type and expressions of von Willebrand Factor and CD31, markers of normal endothelial cells. We obtained the results showing their expression. Thus, possible types of tissues to be regenerated are increased. We will further obtain immortalized clones of other types of cells, and extend the possibility of tissues to be regenerated in vitro.

List of contributions

A. Original Papers

1. Miyazaki, K.[*1,2], Kawamoto, T.[*1], Tanimoto, K., Nishiyama, M., Honda, H.[*2], Kato, Y.[*1] ([*1]Dept. Dent. Med. Biochem., Graduate School of Biomed. Sci., [*2]Dept. Dev. Biol.): Identification of functional hypoxia response elements in the promoter region of the DEC1 and DEC2 genes. J. Biol. Chem., 277(49): 47014-47021, 2002.12. (G)(I)

2．Hiyama, K., Mendoza, C.*1, Hiyama, E.*2 (*1Dept. Mol. Int. Med., Graduate School of Biomed. Sci., *2Dept. General Med., Univ. Hosp.): Non-RI protocols for L-myc allelotyping and deletion mapping of chromosome 1p in primary lung cancers. *In*: Methods in Molecular Medicine, Vol.74, Lung Cancer Vol. 1 (ed. B. Driscoll), pp.231-239, Humana Press Inc., Totowa, NJ, U.S.A., 2003.1.

3．Hiyama, K., Hiyama, E.* (*Dept. General Med., Univ. Hosp.): Detection of telomerase activity in lung cancer tissues. *In*: Methods in Molecular Medicine, Vol. 74, Lung Cancer Vol. 1 (ed. B. Driscoll), pp.401-412, Humana Press Inc., Totowa, NJ, U.S.A., 2003.1.

4．Kumazaki, T.: Detection of mRNA expression and alternative splicing in a single cell. *In*: Methods in Molecular Biology, Vol. 193, RT-PCR Protocol (ed. J. O'Connell), pp.59-64, Humana Press Inc., Totowa, NJ, U.S.A., 2002.7. (G)

5．Kumazaki, T., Sasaki, M., Nishiyama, M., Teranishi, Y.*1, Sumida, H.*2, Mitsui, Y.*3 (*1Dept. Physiol.2, Graduate School of Biomed. Sci., *2Hiroshima Internatl. Univ., *3Natl. Inst. Adv. Ind. Sci. Tech.): Effect of BCL-2 down-regulation on cellular life span. BioGerontol. 3: 291-300, 2002.9. (G) (I)

6．Sasaki, M., Kumazaki, T., Tanimoto, K., Nishiyama, M.: Bcl-2 in cancer and normal tissue cells as a prediction marker of response to 5-fluorouracil. Int. J. Oncol., 22(1): 181-186, 2003.1. (G) (I)

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8．Budhi, A.*1, Hiyama, K., Isobe, T.*1, Oshima, Y.*2, Hara, H.*2, Maeda, H.*1, Kohno, N.*1 (*1Dept. Mol. Int. Med., Graduate School of Biomed. Sci., *2Chugoku Health Administ. Ctr., Nippon Telegraph and Telephone West Corp.): Genetic susceptibility for emphysematous changes of the lung in Japanese. Int. J. Mol. Med., 11(3): 321-329, 2003.3. (I)

9．Teranishi, Y.*1, Sugino, H.*1, Ozono, R.*1, Ishioka, N.*1, Kumazazki, T., Tsuru, H.*2 (*1Dept. Physiol. 2, Graduate School of Biomed. Sci.): Contribution of endogenous vasopressin to regional hemodynamics in borderline hypertensive Hiroshima rats. Hypertens. Res., 25(2): 241-248, 2002.3. (G) (I)

10．Teranishi, Y.*1, Kumazazki, T., Miho, N.*2, Sugino, H.*2, Tsuru, H.*3 (*1Dept.Physiol. 2, Graduate School of Biomed. Sci., *21st Dept. Int. Med., Univ. Hosp., *3Dept. Pharmacol., Toho Univ. School of Med.): Are sodium-dependent V1 receptor and sympathetic nerve activations involved in regulation of blood pressure in borderline-hypertensive Hiroshima rats? Hypertens. Res., 25(5): 763-771, 2002.9. (G) (I)

11．Pereira, T.*, Zheng, X.*, Ruas, J. L.*, Tanimoto, K., Poellinger, L.* (*Karolinska Inst.): Identification of residues critical for regulation of protein stability and the transactivation function of the Hypoxia-inducible Factor-1 α by the von Hippel-Lindau tumor suppressor gene product. J. Biol. Chem., 278(9): 6816-6823, 2003.2. (G) (I)

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14. Nishiyama, M., Kumazaki, T.: Cancer genomics: Genetic polymorphisms and development of new cancer therapy. *Gan-chiryou to Shukushu*（Cancer Ther. Host）, 15(1): 89-94, 2003.1.（in Jpn.）(G)

15. Nishiyama, M., Ukon, K.: Prediction of tumor sensitivity to anticancer agents using cDNA microarray. Iyaku Journal(Med. Drug J.), 39(3): 79-84, 2003.3.（in Jpn.）(G)

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18. Hiyama, K.: Genetic aspects of IL-5 and IL-5R. *Zensoku*（Asthma）, 15(3): 31-35, 2002.7.（in Jpn.）

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22. Noguchi, T., Miura, T.*1, Chujo, M.*1, Arinaga, M.*1, Noguchi, T.*1, Yokoyama, S.*2（*12nd Dept. Surg., *21st Dept. Pathol., Oita Med. Univ.）: A case of posterior mediastinal paraganglioma found incidentally with the onset of spontaneous pneumothorax. *Nihon Rinsho-Geka Gakkai-Zasshi*（J. Jpn. Surg. Assoc.）, 63: 2136-2140, 2002. 9.（in Jpn.）

23. Noguchi, T., Nishiyama, M.: Sensitivity determinants to anticancer agents. Surgery Frontier, 10(1):81-86, 2003.3.(in Jpn.)(G)

24. Noguchi, T.*1, Noguchi, T., Fujiwara, S.*2, Fujiyoshi, K.*3, Kikuchi, R.*1, Uchida, Y.*1（*12nd Dept. Surg., Oita Med. Univ., *2Dept. Surg., Nagato Memorial Hosp., *3Dept. Surg., Oita Prefectual Koseiren Tsurumi Hosp.）: A case of nodular fasciitis of the breast mimicking breast cancer. *Nihon Rinsho-Geka Gakkai-Zasshi*（J. Jpn. Surg. Assoc.）, 63: 1871-1874, 2002.8.（in Jpn.）

25. Fujiwara, S.*1, Suehiro, S.*1, Noguchi, T, Noguchi, T.*2, Uchida, Y.*2（*1Dept. Surg., Nagato Memorial Hosp.,*22nd Dept. Surg., Oita Med. Univ.）: Experience of three cases of skin ulcer well responded to the combination treatment with b FGF and PGE1. *Rinshou to Kenkyuu*（Jpn. J. Clin. Exp. Med., 79: 1680-1682, 2002.9.（in Jpn.）

26. Suehiro, S.*1, Noguchi, T.*2, Fujiwara, S.*1, Kikuchi, R.*2, Noguchi, T., Uchida, Y.*2（*1Dept. Surg., Nagato Memorial Hosp., *22nd Dept. Surg., Oita Med. Univ.）: A case of incarcerated omphalocele with decompensated liver cirrhosis. *Nihon-Gekagakkai Rengou Gakkaishi*（J. Jpn. College Surg.）, 27: 913-915, 2002.12.（in Jpn.）

B. Meeting Presentations

1. Nishiyama, M.: Developmental research of tailored medicine for colorectal cancer. 11th Biennial Congress of Internatl. Soc. Univ. Colon & Rectal Surg., "Luncheon Seminar", Osaka, 2002.4.（G）

2．Nishiyama, M.: Prediction of sensitivity of gastrointestinal cancers to paclitaxel and docetaxel by cDNA microarray analysis. 18th UICC Internatl. Cancer Congress, Oslo, Norway, 2002.6.（G）

3．Hiyama, K., Yoshikawa, M.*, Budhi, A.*, Isobe, T.*, Awaya , Y.*, Kohno, N.*（*Dept. Mol. Int. Med., Graduate School of Biomed., Sci.）: Genetic polymorphisms and severity of chronic obstructive pulmonary disease（COPD）in Japanese. 26th Internatl. Congress of Int. Med., Kyoto, 2002.5.

4．Kumazaki, T., Sasaki, M., Nishiyama, M., Mitsui, Y.*（*Natl. Inst. Adv. Ind. Sci. Tech.）: Overexpression of Bcl-2 enhances death frequency of normal fibroblasts and results in life span shortening. 2002 Conference of the Soc. Korean Gerontol., Seoul, Korea, 2002.7.（G）

5．Tanimoto, K., Yoshiga, K.*1, Poellinger, L.*2, Nishiyama, M.（*1Div.Front. Med. Sci., Graduate School of Biomed. Sci., *2Karolinska Inst.）: Genetic polymorphisms of the hypoxia-inducible factor-1 α gene in head and neck squamous cell carcinomas. 93rd Annual Meeting of Am. Assoc. Cancer Res., San Francisco, U.S.A., 2002.4.（G）

6．Tanimoto, K., Yoshiga, K.*1, Eguchi, H.*2, Imai, K.*2, Nakachi, K.*2, Kaneyasu, M., Ukon, K., Oue, N.*3, Yasui, W.*3, Nishiyama, M.（*1Div. Front. Med. Sci., Graduate School of Biomed. Sci., *2Dept. Radiobiol./ Mol. Epidemiol., *3Dept. Mol. Pathol., Graduate School of Biomed. Sci.）: Single nucleotide polymorphisms enhance the transactivation capacity of hypoxia-inducible factor-1α. 12th Internatl. Symposium of the Hiroshima Cancer Seminar, Hiroshima, 2002.11.（G）

7．Sasaki, M., Kumazaki, T., Tanimoto, K., Nishiyama, M.: Bcl-2 in cancer and normal tissue cells as a prediction marker of response to 5-fluorouracil. 12th Internatl. Symposium of the Hiroshima Cancer Seminar, Hiroshima, 2002.11.（G）

8．Ukon, K., Tanimoto, K., Toge, T.*, Nishiyama, M.（*Dept. Surg. Oncol.）: Mechanisms of transcriptional regulation of dihydropyrimidine dehydrogenase gene. 12th Internatl. Symposium of the Hiroshima Cancer Seminar, Hiroshima, 2002.11.（G）

9．Endo, W.*1, Sekikawa, T.*1, Yamamoto, W.*2, Nakamura, A.*1, Yasuhara, H.*2, Nishiyama, M., Matsukawa, M.*1, Kurihara, M.*1, Shimada, K.*1（*1Dept. Gastroenterol., Toyosu Hosp., Showa Univ., *2Dept. Phamacol., School of Med., Showa Univ.）: Absorption of the active metabolite SN-38 increased with P-glycoprotein inhibitors on the human pharmaco-physiological dosing in the intestinal cell model. 93rd Annual Meeting of Am. Assoc. Cancer Res., San Francisco, U.S.A., 2002.4.（G）

10．Yoshida, K.*1, Hirbayashi, N.*2, Takiyama, W.*2, Ninomiya, M.*3, Takakura, N.*3, Sakamoto, J.*4, Nishiyama, M., Toge, T.*1（*1Dept. Surg. Oncol., *2Dept. Surg., Hiroshima City Asa Hosp., *3Dept. Surg. Hiroshima City Hosp., *4Dept. Epidemiol. Clin. Res. Info. Management, Graduate School of Med., Kyoto Univ.）: Japanese experience in combining S1 and Taxotere®（docetaxel）. Internatl Clin. Update Meeting on Gastrointest. Cancer, Cheju, Korea, 2002.9.（G）

11．Hiyama, E.*1, Hiyama, K., Yokoyama, T.*1, Takahashi, N.*2（*1Dept. General Med., Univ. Hosp., *2Dept. Genet., Rad. Effects Res. Found.）: Array CGH analysis in human neuroblastoma. 93rd Annual Meeting of Am. Assoc. Cancer Res., San Francisco, U. S. A., 2002.4.

12．Hiyama, E.*, Hiyama, K., Yokoyama, T.*（*Dept. General Med., Univ. Hosp.）: Gene expression profiling of human neuroblastoma. 38th Annual Meeting of the Am. Soc. Clin. Oncol., Orlando, U. S. A., 2002.5.

13. Hiyama, E.*, Hiyama, K.(*Dept. General Med., Univ. Hosp.): Clinical utility of telomerase in solid tumors. United States-Japan Cooperative Cancer Res. Program. Maui, U.S.A., 2002.8.

14. Hiyama, E.*1, Hiyama, K., Reynolds, C.P.*2, Shay, J.W.*3, Yokoyama, T.*1 (*1Dept. General Med., Univ. Hosp., *2Child. Hosp. Los Angeles, *3Univ. Texas Southwest. Med. Ctr.): Expression profiling of neuroblastomas with high telomerase activity and low telomerase activity. Am. Assoc. Cancer Res. Special Conference in Cancer Res., San Francisco, U.S.A., 2002.12.

15. Kato, T.*, Noguchi, T.*, Wada, S.*, Takeno, S.*, Kudo, T.*, Noguchi, T., Moriyama, H.*, Hashimoto, T*, Uchida, Y*(*2nd Dept. Surg., Oita Med. Univ.): Surveillance for double cancer in patients with esophageal cancer. 48th Annual Congress of Jpn Section of Internatl. College of Surg., Okayama, 2002. 6.

16. Kimura, Y.*, Noguchi, T.*, Chujo, M*, Takeno, S.*, Shibata, T.*, Noguchi, T., Fumoto, S.*, Uchida, Y.* (*2nd Dept. of Surg., Oita Med. Univ.): Chromosomal imbalances in esophageal cancer analyzed by CGH. 20th Annual Meeting & 15th Internatl. Symposium of Jpn. Human Cell Soc., Tokyo, 2002.8. (G)

17. Nishiyama, M.: Development of new cancer therapy using cDNA microarray. Special Symposium "Progress in genomic technology and surgery" (invited), 102nd Annual Meeting of Jpn. Surg. Soc., Kyoto, 2003.4. (G)

18. Nishiyama, M.: Personalized medicine for gastrointestinal cancers and Pharmacogenomics. Workshop 2 "Individualized medicine and new genomics" (invited), 18th Annual Meeting of Jpn. Soc. of Drug Delivery System, Sapporo, 2002.6. (G)

19. Nishiyama, M.: Dihydropyrimidine dehydrogenase (DPD) gene and tailored chemotherapy using 5-fluorouracil. Evening Seminar (invited), 13th Annual Meeting of Jpn. Soc. Gastroenterol. Carcinogenesis, Osaka, 2002.9. (G)

20. Nishiyama, M.: Tailored chemotherapy: Development of epoch-making cancer treatment. Special Lecture (invited), 53rd Annual Meeting of Hiroshima branch of Jpn. Soc. Obst. Gynecol., Fukuyama, 2002.9. (G)

21. Nishiyama, M.: Cancer and its therapy. Special lecture (invited). 19th Seminar for Health, Hiroshima, 2002.9. (G)

22. Nishiyama, M.: Identification of new molecular targets of cancer by genome-wide complementary DNA analysis and its clinical application, Special lecture (invited), 5th Symposium on Sensitization of Cancer Treat. in Nara, Nara, 2003.2. (G)

23. Nishiyama, M.: Genomics and anticancer chemotherapy in new era. Special lecture (invited), 20th Annual Meeting of the Oita Cancer Chemother., Oita, 2003.3. (G)

24. Nishiyama, M.: Prediction of individual response to anticancer agents and identification of novel target for drug development. Invited lecture, 2003 Tokyo Cancer Forum, Tokyo, 2003.3. (G)

25. Hiyama, K., Ikegami, Y.*, Kohno, N.* (*Dept. Mol. Int. Med., Graduate School. Biomed. Sci.): Genetic aberrations responsible for the activation of telomerase in lung cancer. 42nd Annual Meeting of Jpn. Resp. Soc., Sendai, 2002.4.

26. Hiyama, K.: Bedside genomics. Invited Lecture, Academic Lecture Meeting of Iwakuni Med. Assoc., Iwakuni, 2003.1.

27. Kumazaki, T., Sasaki, M., Nishiyama, M., Mitsui, Y.* (*Natl. Inst. Adv. Ind. Sci. Tech.): Shortening of cellular life span

by overexpression of BCL-2. 25th Annual Meeting of Jpn. Biomed. Gerontol., Tsukuba, 2002.5.（G）

28. Tanimoto, K., Ukon, K., Noguchi, T., Kaneyasu, M., Nishiyama, M.: Aberrant hypermetylation of dihydropyrimidine dehydrogenase（DPD）gene. 61st Annual Meeting of Jpn. Cancer Assoc., Tokyo, 2002.10.（G）

29. Tanimoto, K., Yoshiga, K.*1, Eguchi, H.*2, Imai, K.*2, Nakachi, K.*2, Nishiyama, M.（*1Div. Front. Med. Sci., *2Dept. Radiobiol./Mol. Epidemiol. Graduate School of Biomed., Sci.）: Molecular epidemiological analysis of single nucleotide polymorphisms of Hypoxia-Inducible Factor-1α gene in head and neck squamous cell carcinomas. 3rd Annual Meeting of Jpn. Soc. Cancer Mol. Epidemiol., Kagoshima, 2002.5（G）

30. Tanimoto, K., Yoshiga, K.*1, Eguchi, H.*2, Imai, K.*2, Nakachi, K.*2, Nishiyama, M.（*1Div. Front. Med. Sci., *2Dept. Radiobiol./ Mol. Epidemiol., Graduate School of Biomed. Sci.）: Modulation of Hypoxia-Inducible Factor-1α Transactivation by Two Single-nucleotide Polymorphisms: An Implication in Clinical Significance. 6th Annual Meeting of Jpn. Soc. of Mol. Target Ther., Sapporo, 2002.6（G）

31. Tanimoto, K., Yoshiga, K.*1, Lorenz Poellinger*2, Nishiyama, M.（*1Div. Front. Med. Sci., Graduate School of Biomed. Sci., *2Karolinska Inst.）: Conditional regulation of the HIF-1α by tumor suppressor proteins. 3rd Congress of Hormone and Cancer, Sendai, 2002.8（G）

32. Tanimoto, K., Yoshiga, K.*（*Div. Front. Med. Sci., Graduate School of Biomed. Sci.）: Single-nucleotide polymorphisms of HIF-1α gene in head and neck squamous cell carcinomas. The 47th Annual Meeting of Jpn. Soc. Oral Maxillofac. Surg., Sapporo, 2002.10（G）

33. Tanimoto, K., Yoshiga, K.*1, Eguchi, H.*2, Imai, K.*2, Nakachi, K.*2, Oue, N.*3, Yasui, W.*3, Nishiyama, M.（*1Div. Front. Med. Sci., *2Dept. Radiobiol./Mol. Epidemiol., *3Mol. Pathol., Graduate School of Biomed. Sci.）: Single-nucleotide polymorphisms of hypoxia-inducible factor-1α gene in solid tumors. 25th Annual Meeting of Mol. Biol. Soc. Jpn., Yokohama, 2002.12（G）

34. Sasaki, M., Kumazaki, T., Mitsui, Y.*, Nishiyama, M.（*Natl. Inst. Adv. Ind. Sci. Tech.）: Effect of Bcl-2 on sensitivity to anti-cancer drug of normal fibroblasts. 61st Annual Meeting of Jpn. Cancer Assoc., Tokyo, 2002.10.（G）

35. Ukon, K., Tanimoto, K., Toge, T.*, Nishiyama, M.（*Dept. Surg. Oncol.）: Transcriptional regulation mechanisms of dihydropyrimidine dehydrogenase（DPD）gene. 11th Annual meeting of Jpn. Soc. Strategies Cancer Res. Treat., Tokyo, 2002.6.

36. Ukon, K., Tanimoto, K., Toge, T.*, Nishiyama, M.（*Surg. Oncol.）: Analysis of mechanisms of transcriptional regulation of dihydropyrimidine dehydrogenase（DPD）gene. 61st Annual Meeting of Jpn. Cancer Assoc., Tokyo, 2002.10.（G）

37. Noguchi, T., Noguchi, T.*, Wada, S.*, Takeno, S.*, Hashimoto, T.*, Moriyama, H.*, Kudo, T.*, Tohara, K.*,Uchida, Y.*（*2nd Dept. Surg., Oita Med. Univ.）: Strategy for Surgical Esophageal Carcinoma. 35th Annual Kyusyu-Branch Meeting of the Jpn. Assoc. for Thoracic Surg., Fukuoka, 2002.7.

38. Noguchi, T., Tanimoto, K., Ukon, K., Hiyama, K., Nishiyama, M., Noguchi, T.*, Uchida, Y.*（*2nd Dept. Surg., Oita Med. Univ.）: Aberrant hypermethylation of *dihydropyrimidine dehydrogenase*（*DPYD*）promoter region and its role in 5-FU response. 20th Annual Meeting of the Oita Cancer Chemother., Oita, 2003.3.（G）

39. Noguchi, T., Tanimoto, K., Ukon, K., Hiyama, K., Noguchi, T.*, Uchida, Y.*, Nishiyama, M. (*2nd Dept. Surg., Oita Med. Univ.): Role of aberrant hypermethylation of *dihydropyrimidine dehydrogenase* (*DPYD*) promoter region in 5-FU chemotherapy. 36th Meeting of Res. Soc. for sensitivity of Cancer, Okayama, 2003.3. (G)

40. Suzuki, F.*, Sasai, K.*, Akimoto, Y.*, Miyaji, R.*, Yajima, H.*, Nishiyama, M. (*Dept. Regul. Radiobiol.): Caspase-independent apoptosis induction of HeLa S3cells by UV. 45th Annual Meeting of the Jpn. Rad. Res. Soc., Sendai, 2002.9. (G)

41. Otani, K.*1, Ohtaki, M.*2, Satoh, K.*2, Nishiyama, M., (*1Jpn. Biol. Info. Consort., *2Dept. Environmetr. Biometr.): Normalization of expression signals in cDNA microarray analysis. 16th Symposium of Jpn. Soc. Computational Statist., Nagasaki, 2002.10. (G)

42. Yoshida, K.*1, Hirabayashi, N.*2, Takiyama, W.*2, Ninomiya, M.*3, Takakura, N.*3, Sakamoto, J.*4, Nishiyama, M., Toge, T.*1 (*1Dept. Surg. Oncol., *2Dept. Surg., Hiroshima City Asa Hosp., *3Dept. Surg., Hiroshima City Hosp., *4Dept. Epidemiol. Clin. Res. Info. Management, Graduate School of Med., Kyoto Univ.): Phase I clinical trial of combination of TS-1 with Docetaxel in metastatic gastric cancer. 64th Annual Meeting of Jpn. Soc. Clin. Surg., Tokyo, 2002.11. (G)

43. Budhi, A.*1, Hiyama, K., Isobe, T.*1, Oshima, Y.*2, Hara, H.*2, Kohno, N.*1 (*1Dept. Mol. Int. Med. Graduate School of Biomed. Sci., *2Chugoku Health Administ. Ctr., Nippon Telegraph and Telephone West Corp.): Association between emphysematous changes and genetic polymorphisms in Japanese. 42nd Annual Meeting of Jpn. Respiratory Soc., Sendai, 2002.4.

44. Kawamoto, T.*1, Honma, S.*3, Miyazaki, K.*1,2, Fujimoto, K.*1, Sato, F.*1, Hamaguchi, H.*1, Tanimoto, K., Honma, K.*3, Noshiro, M.*1, Kato, Y.*1 (*1Dept. Dent. Med. Biochem., Graduate School of Biomed. Sci., *2Dept. Dev. Biol., *3Dept. Physiol., Graduate School of Med., Hokkaido Univ.): The roles of bHLH transcription factores DECs in adaptation to hypoxia and circadian rhythm. 25th Annual Meeting of Mol. Biol. Soc. Jpn., Yokohama, 2002.12.

45. Kumagai, K.*, Hiyama, K., Awaya, K.*, Kohno, N.* (*Dept. Mol. Int. Med., Graduate School of Biomed. Sci.): Genetic polymorphisms associated with the sensitivity to immunosuppressive drugs in rheumatic diseases. 46th Annual Meeting of the Jpn. College of Rheumatol., Kobe, 2002.5.

46. Sasaki, K.*1, Tsuyama, N.*2, Kodaira, M.*1, Itoh, M.*1, Sugita, K.*1, Katayama, H.*1, Fujiyama, A.*3, Hiyama, K., Hiyama, E.*4, Takahashi, N.*1 (*1Dept. Genet., Rad. Effects Res. Found., *2Appl. Med. Engin. Sci., Yamaguchi Univ., *3Natl. Inst. Info., *4Dept. General Med., Univ. Hosp.): Study of genetic effects of atomic-bomb radiation by using microarray-based comparative genomic hybridization (array CGH)-Preliminary experiment-. 43rd Annual Meeting of Res. Soc. Delayed Effects of Atomic Bomb Detonation, Nagasaki, 2002.6.

47. Takahashi, N.*1, Sasaki, K.*1, Tsuyama, N.*2, Kodaira, M.*1, Sugita, K.*1, Katayama, H.*1, Hiyama, K., Hiyama, E.*3 (1Dept. Genet., Rad. Effects Res. Found.,*2 Appl. Med. Engin. Sci., Yamaguchi Univ., *3Natl. Inst. Info., *3Dept. General Med., Univ. Hosp.): Application of microarray-based comparative genomic hybridization (array CGH) on the study of genetic effects of atomic-bomb radiation. 45th Annual Meeting of the Jpn. Rad. Res. Soc., Sendai, 2002.9.

48. Takahashi, N*1, Sasaki, K.*1, Tsuyama, N.*2, Kodaira, M*1, Miura, A.*1, Sugita, K.*1, Katayama, H.*1, Oomine, H.*1, Shimoichi, Y.*1、Imanaka, M.*1, Hiyama, K., Hiyama, E.*3 (*1Dept. Genet., Rad. Effects Res. Found.,*2 Appl. Med. Engin. Sci., Yamaguchi Univ., *3Natl. Inst. Info., *3Dept. General Med., Univ. Hosp.): Genome-wide analysis using microarray-

based comparative genomic hybridization（array CGH）: Report 2. 47th Annual Meeting of the Jpn. Soc. Human Genet., Nagoya, 2002.11.

49. Hiyama, E.*1, Yokoyama, T.*1, Yamaoka, H.*2, Hiyama, K.（*1Dept. General Med., *21st Dept. Surg., Univ. Hosp.）: Clinical application of microarray technique in pediatric malignant tumors. 64th Annual Meeting of Jpn. Soc. for Clin. Surg., Tokyo, 2002.11.

50. Hiyama, E.*1, Yokoyama, T.*1, Hiyama, K., Sato, T.*2, Nishimura, S.*2, Ueda, K.*2（*1Dept. General Med., *2Dept. Pediat., Univ. Hosp.）: Molecular analysis as a translational research on pediatric solid tumors. Symposium 2: "Update of translational research on the treatment of pediatric solid tumors", 18th Annual Meeting of Jpn. Soc. Pediat. Oncol., Fukuoka, 2002.11.

51. Ikegami, Y.*, Hiyama, K., Kohno, N.*（*Dept. Mol. Int. Med., Graduate School of Biomed. Sci.）: *HPS1* gene analysis in a patient with Hermansky-Pudlak syndrome（HPS）. 2nd Meeting of the Lung Mol. Biol. Conference, Fukuoka, 2003.1.

52. Yoshiga, K.*1, Tanimoto, K., Eguchi, H.*2, Imai, K.*2, Nakachi, K.*2, Nishiyama, M.（*1Div. Front. Med. Sci., *2Dept. Radiobiol./Mol. Epidemiol., *3Mol. Pathol., Graduate School of Biomed. Sci.）: Single-nucleotide polymorphisms of hypoxia-inducible factor-1α gene in head and neck squamous cell carcinomas. 61st Annual Meeting of Jpn. Cancer Assoc., Tokyo, 2002.10（G）

53. Miyazaki, K.*1,2, Kawamoto, K.*2, Tanimoto, K., Honda, H.*1, Kato, Y.*2（*1Dept. Dev. Biol., *2Dept. Dent. Med. Biochem., Graduate School of Bio. Med. Sci.）: Hypoxia increases gene expression of DEC1 and DEC2 and identification of a hypoxia response element bound to HIF-1 in the DEC1 and DEC2 genes. 5th Annual Meeting of Mol. Biol. Soc. Jpn., Yokohama, 2002.12.（G）

54. Shibata, T.*, Noguchi, T.*, Takeno, S.*, Fumoto, S.*, Noguchi, T., Wada, S.*, Moriyama, H.*, Uchida, Y.*（*2nd Dept. Surg., Oita Med. Univ.）: DNA-PKcs expression in esophageal cancer; as a predictor for chemoradiation therapeutic sensitivity. The 102nd Annual Meeting of Jpn. Surg. Soc., Kyoto, 2002.4.

55. Moriyama, H.*, Noguchi, T.*, Tohara, K.*, Hashimoto, T.*, Wada, S.*, Takeno, S.*, Noguchi, T, Kudo, T.*, Kikuchi, R.*, Uchida, Y.*（*2nd Dept. Surg., Oita Med. Univ.）: A case of primary extrameduliary plasmacytoma of the small intestine. 79th Annual Kyusyu-Branch Meeting of the Jpn. Soc. Gastroenterol., Kurume, 2002.5.

56. Kudo, T.*, Noguchi, T.*, Hashimoto, T.*, Moriyama, H.*, Wada, S.*, Takeno, S.*, Noguchi, T., Tohara, K.*, Kikuchi, R.*, Uchida, Y.*（*2nd Dept. Surg., Oita Med. Univ.）: A case of inoperable advanced gastric cancer with long survival period which was led by TS-1 chemotherapy. 79th Annual Kyusyu-Branch Meeting of the Jpn. Soc. of Gastroenterol., Kurume, 2002.5.

57. Kato, T.*, Noguchi, T.*, Wada, S.*, Takeno, S.*, Kudo, T.*, Noguchi, T., Moriyama, H.*, Hashimoto, T.*, Uchida, Y.*（*2nd Dept. Surg., Oita Med. Univ.）: Head and neck cancer in the patient with superficial esophageal cancer. 47th Annual Meeting of Jpn. Res. Soc. Early Esophageal Cancer and Chromoendscopy, Hiroshima, 2002.7.

58. Wada, S.*, Noguchi, T.*, Takeno, S.*, Kato, T.*, Moriyama, H.*, Hashimoto, T.*, Kudo, T.*, Noguchi, T, Tohara, K.*, Uchida, Y.*（*2nd Dept. Surg., Oita Med. Univ.）: Lymph node dissection for carcinoma around the esophagogastric junction. 35th Annual Kyusyu-Branch Meeting of the Jpn. Assoc. Thoracic Surg., Fukuoka, 2002.7.

59. Shimizu, M.*1, Fujiwara, S.*2, Noguchi, T., Kawano, K.*3 (*1Dept. Oral and Maxillofac. Surg., Nagato Memorial Hosp., *2Dept. Surg., Nagato Memoria Hosp., *3Dept. Oral and Maxillofac. Surg., Oita Med. Univ.): A case of oncological and labioplastical surgery for polymorphic adenoma of the upper labra. 22nd Seminar of Soc. of Ochanomizu Med., Tokyo, 2002.8.

60. Kimura, Y.*, Noguchi, T.*, Chujo, M.*, Takeno, S.*, Shibata, T.*, Noguchi, T., Fumoto, S.*, Uchida, Y.* (*2nd Dept. Surg., Oita Med. Univ.): Detection of chromosomal abnormality in esophageal cancer using CGH method. 13th Annual Meeting of Jpn. Soc. Gastroenterol. Carcinogenesis, Osaka, 2002.9. (G)

61. Kato, T.*, Noguchi, T.*, Hashimoto, T.*, Wada, S.*, Takeno, S.*, Kudo, T.*, Noguchi, T., Tohara, K.*, Uchida, Y.* (*2nd Dept. Surg., Oita Med. Univ.): Small cell carcinoma of the esophagus; a clinicopathological and immunohistochemical analysis of six cases. 13th Annual Meeting of Jpn. Soc. Gastroenterol. Carcinogenesis, Osaka, 2002.9.

62. Noguchi, T.*, Wada, S.*, Takeno, S.*, Kato, T.*, Moriyama, H.*, Hashimoto, T.*, Kudo, T.*, Noguchi, T., Tohara, K.*, Uchida, Y.* (*2nd Dept. Surg., Oita Med. Univ.): Two-step three field lymph node dissection for thoracic esophageal carcinoma. Symposium "Treatment strategy and outcome in advanced esophageal cancer", 55th Annual Meeting of Jpn. Assoc. Thoracic Surg., Fukuoka, 2002.10.

63. Wada, S.*, Noguchi, T.*, Takeno, S.*, Kato, T.*, Moriyama, H.*, Hashimoto, T.*, Kudo, T.*, Noguchi, T., Tohara, K.*, Uchida, Y.* (*2nd Dept. Surg., Oita Med. Univ.): Clinicopathological study of carcinoma around the esophagogastric junction. 55th Annual Meeting of the Jpn. Assoc. Thoracic Surg., Fukuoka, 2002.10.

C. Others

1. Yasui, W.*1, Nishiyama, M., Tsuruo, T.*2, Tahara, E.*3 (*1Dept. Mol. Pathol., Graduate School of Biomed. Sci., *2Lab. Cell Growth and Regul., Inst. Mol. Cell. Biosci., Univ. of Tokyo, *3Rad. Effects Res. Found.): Molecular targeting therapy for cancer: The Twelfth International Symposium of the Hiroshima Cancer Seminar, November 2002. Cancer Sci. (Jpn. J. Cancer Res.), 94(2): 221-223, 2003.2.

2. Nishiyama, M.: Tailored medicine. 19th Meeting of Soc. Gynecol. Cancer Chemother., Meeting Report (2002.1.), 5-15, 2002.7. (in Jpn.) (G)

3. Nishiyama, M.: Individualized cancer chemotherapy. 15th Academic meeting of Hyogo Res. Soc. P.O. Chemother. Meeting Report (2002.1.), 5-15, 2002.11. (in Jpn.) (G)

4. Sasaki, K.*1, Tsuyama, N.*2, Kodaira, M.*1, Itoh, M.*1, Sugita, K.*1, Katayama, H.*1, Fujiyama, A.*3, Hiyama, K., Hiyama, E.*4, Takahashi, N.*1 (*1Dept. Genet., Rad. Effects Res. Found., *2Appl. Med. Engin. Sci., Yamaguchi Univ., *3Natl. Inst. Info., *4Dept. General Med., Univ. Hosp.): Study of genetic effects of atomic-bomb radiation by using microarray-based comparative genomic hybridization (array CGH)-Preliminary experiment-. Nagasaki Medical Journal. 77 (Suppl.): The 43rd Annual Meeting of Res. Soc. Delayed Effects of Atomic Bomb Detonation, Nagasaki (2002.6), 158-162, 2002.9. (in Jpn.)

5. Nishiyama, M.: For good health- Informative society and health. Broadcasting Open College Program 2002, Hiroshima Univ., RCC TV, 2002.10.

6. Nishiyama, M.: Pharamacogenomics for development of new anticancer therapy. Special Lecture Program in Graduate school of Med., Univ. Occup. Environ. Health, 2003.2. (G)

7．Nishiyama, M.: Novel stream in anticancer chemotherapy for gastrointestinal cancers- tailored medicine-. Special Lecture Program in Graduate school of Med., Kobe Univ., 2003.2.（G）

（R），（A），（G）and（C）are reports on the study using Radiation Experiments, Animal Experiments, Gene Technology Facilities and Studies established at the International Radiation Information Center, respectively.（I）indicates printed in the scientific journals listed in Current Contents.