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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 genetic and molecular basis underlying variable drug response among patients, and developing new anticancer treatments, molecular target therapy and personalized medicine. We have surveyed DNA and RNA variation using a variety of technologies such as cDNA microarray, oligoarray, and real-time RT-PCR, 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 2005 as follows:

1. Development of personalized anticancer chemotherapies
   1) Prospective clinical studies on pharmacogenetics
   2) Development of concise prediction models of individual therapeutic response to anticancer drugs based on pharmacogenomics
      a) Colo-rectal and stomach cancers
      b) Esophageal cancer
      c) Ovarian cancer
2. Genomics-based drug discovery and molecular target therapy for chemotherapy-resistant solid tumors
   1) Esophageal cancer
   2) Endometrial carcinoma
   3) Telomere 3'-overhang and chemosensitivity to anticancer drugs
   4) Genes responsible for cellular immortalization common in various human cancers
   5) Pancreatic cancer

3. Molecular mechanisms of hypoxic response in solid tumors
   1) Transgenic mice of the human hypoxia-inducible factor-1 α gene
   2) Transcriptional regulation of the mismatch repair gene hMLH1 under hypoxic conditions
   3) Molecular mechanisms of resistance to chemotherapy and irradiation in oral cancer cells under hypoxic conditions
   4) Transcriptional protein complexes of HIF-1


With respect to personal affairs, Dr. S. Fumoto, Dr. K. Nishigami, and Mr. S. Akitomo have started their researches as a postgraduate student since Apr. 1/2005. Dr. Marina Arifin (Research Fellow) joined our research projects since Oct.1 2005, and Dr. M. Tsugane (Research Fellow) has finished to learn several experimental techniques and methodologies to discover novel molecular target for drug development (-Sep. 2005). Dr. M. Komatsu and Mr. Y. Nishimura were awarded the degree of Doctor and Master for medical science, respectively, and Dr. K. Tanimoto won a MEDARTIS Award at 50th Annual meeting of Japanese Society of Oral and Maxillofacial Surgeons.

We had a total of 20 presentations at symposium, invited, educational, and special lectures in this year. Prof. M. Nishiyama was appointed as members of “Council member of the Japanese Cancer Association”, “Director, Chairman of Educational committee, Vice-chairman of Committee for Certification of Clinical Oncologist and Committee its System Establishment, Member of Editorial Committee of the Japan Society of Clinical Oncology”, “Council of Japanese Society of Medical Oncology”, “Council of the Japanese Gastric Cancer Society”, “Council of Japanese Society of Gastroenterological Carcinogenesis”, “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 “Vice President, Board of Ethical Committee,
1. Development of personalized anticancer chemotherapies

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 polymorphism, mutation and gene expression analyses.

1) Prospective clinical studies on pharmacogenetics

Akitomo, S., Tanimoto, K., Hiyama, K., Nishiyama, M.

Purpose: To identify the useful markers for prediction of individual’s response to drug, pharmacogenetic studies were performed as several prospective clinical trials.

Methods and Results: Identification of DNA variants of drug metabolic enzyme genes, such as CYP3A4, CYP2C8, and UGT1A1, was studied in samples from cancer patients to understand the link between individual’s genetic make-up and their response to drug therapy. We have started a pharmacogenetic study combined with phase II clinical evaluation of paclitaxel weekly administration for metastatic gastric cancer and irinotecan (CPT-11) single administration for colo-rectal cancers as adjuvant setting. Our clinical studies have provided a lot of useful information, and we found novel polymorphisms in the promoter region of CYP2C8 and close relationship between CESIA2 expression and in vitro CPT-11 activity.

2) Development of concise prediction models of individual therapeutic response to anticancer drugs based on pharmacogenomics

a) Colo-rectal and stomach cancers

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

Purpose: To realize personalized anticancer chemotherapies, we have attempted to demonstrate the clinical accuracy of prediction system of individual therapeutic efficacy.

Methods and Results: Applying the candidate chemosensitivity prediction marker genes selected by in vitro microarray analyses and MTT assays, we could develop clinical chemosensitivity prediction models using their expression data in the cancer tissues obtained from colo-rectal cancer patients who underwent the protocol of irinotecan (CPT-11) single administration as adjuvant setting. The development of prediction model for gastric cancer patients who underwent the phase II clinical evaluation of paclitaxel weekly administration is ongoing.

b) Esophageal cancer

Fumoto, S., Komatsu, M., Tanimoto, K., Hiyama, K., Nishiyama, M.

Purpose: Esophageal cancer is a highly lethal disease and the optimal therapy remains unclear. Since chemotherapy
gives a better chance of survival, we attempted to identify novel marker genes and develop a chemosensitivity prediction model to improve individual response to the therapy.

**Methods and Results:** We have performed comprehensive gene expression analyses (cDNA and oligonucleotide microarrays) and MTT assay of 8 drugs in 20 KYSE squamous cell carcinoma cell lines to sort out candidate marker genes whose expression levels reproducibly correlated with cellular drug sensitivities by both microarray analyses. From the first candidates, we selected 3 different sets of genes as the potent prediction markers: They are 1) better marker genes known as drug sensitivity determinants, 2) novel predictive genes highly correlative with drug sensitivity, 3) another novel genes selected through additional mathematical method, a two-dimensional mixed normal model using oligomicroarray expression data. After confirmation with real-time RT-PCR, we then performed multiple regression analyses to develop drug-sensitivity prediction formulae using the quantified expression data of selected marker genes. Using the same sets of genes, we also constructed the prediction models for individual clinical response to 5-FU-based chemotherapy using 18 cases. We could develop highly predictive formulae of in vitro sensitivities to the 4 drugs and clinical responses to 5-FU-based adjuvant chemotherapies in terms of overall and disease-free survivals. Our selected genes are likely better drug-sensitivity markers and formulae using the novel genes would provide advantages in prediction. To confirm the functional roles of these candidate marker genes, we constructed expression vectors, transfected to esophageal cancer cell lines, and evaluated the effects on chemosensitivity. We are now planning the prospective clinical study to confirm the feasibility of these prediction models.

c) Ovarian cancer

Komatsu, M., Hiyama, K., Yunokawa, M., Tanimoto, K., Nishiyama, M.

**Purpose:** The selection of an optimal chemotherapeutic regimen to each individual is of key importance to improve the poor prognosis in ovarian cancer. To realize personalized medicine in ovarian cancer chemotherapy, we are going to attempt to select prediction marker genes and develop prediction models for efficacy of anticancer drugs. First we tried to identify useful prediction marker genes for paclitaxel and cisplatin responses.

**Methods and Results:** We attempted to identify potent marker genes using a new statistical analysis, and developed a prediction system for individual response to platinum/paclitaxel (TXL) combination chemotherapy in ovarian cancer patients, based on the hypothesis that expression analysis of a set of the key drug sensitivity genes for platinum and TXL could allow us to predict therapeutic response to the combination. From 10 human ovarian cancer cell lines, genes correlative in the expression levels with cytotoxicities of cisplatin (CDDP) and TXL were chosen. We first selected 5 reliable prediction markers for the 2 drugs from 22 genes already known as sensitivity determinants, and then identified another 8 novel genes through a two-dimensional mixed normal model using oligomicroarray expression data. Using expression data of genes quantified by real-time RT-PCR, we fixed the best linear model, which converted the quantified expression data into an IC<sub>50</sub> value of each drug. Multiple regression analysis of the selected genes yielded 3 prediction formulae for in vitro activity of CDDP and TXL. In the same way, using the same genes selected in in vitro, we then attempted to develop prediction formulae for progression-free survival to the platinum/TXL combination. We therefore constructed possible formulae using different sets of 13 selected marker gene (5 known and 8 novel genes): Utility-confirmation analyses using another 9 test samples appeared to show that the formulae using a set of 8 novel marker genes alone could accurately predict PFS (r=0.683, P=0.042).

d) Lung cancer

Marina Arifin, Hiyama, K., Tanimoto, K., Nishiyama, M.

**Purpose:** Since prognosis of patients with unresectable lung cancer remains poor, it is urgent to explore the chemosensitivity prediction markers and develop the individualized chemotherapy based on them. Although mutation in
EGFR is a candidate marker to predict gefitinib efficacy in NSCLC, exceptional cases exist. We are trying to clarify the biological significance of these aberrations.

**Methods and Results:** We examine the genetic variations in *EGFR* and analyze the relationship with chemosensitivities and expression profiles in lung cancer cell lines. We also examine the *EGFR* mutations in lung cancer tissues and compare with other molecular features such as aberrations on oncogenes and tumor suppressor genes, telomerase activity, telomere length, etc. We have established the experimental protocols and are now searching the *EGFR* mutations.

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

1) **Esophageal cancer cells**

   Hiyama, K., Nishimura, Y., Tanimoto, K., Nishiyama, M.

   **Purpose:** Stability of telomere in corporation with telomerase is indispensable for the cellular immortalization in esophageal cancer cells. For the new anti-cancer strategy, we explored the genes responsible for the regulation of telomerase in esophageal cancer cells.

   **Methods:** 1) Terminal restriction fragment (TRF) lengths of human esophageal cancer cell lines are analyzed by Southern blotting. 2) The expression levels analyzed by using oligonucleotide microarray were compared between esophageal cancer cell lines and non-cancerous epithelial cell strains, and between telomere elongated cell lines and the shorted ones. 3) The candidate immortalization-regulating gene expression vector was constructed, transfected to esophageal cancer cell lines, and effects on their phenotype were observed.

   **Results:** In most of the esophageal cancer cell lines, 196 and 392 genes showed more than two-fold higher or lower expression than those of the non-cancerous epithelial cell strains, respectively. Among them, over expression of the gene that was commonly repressed specifically in esophageal cancer cell lines caused reduction of cloning efficacy, change in form (flat and large), and growth suppression. This gene is expected to be a novel tumor suppressor gene for esophageal cancer.

2) **Endometrial carcinoma**

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

   **Purpose:** While normal endometrial tissues show telomerase activity, the level is lower than that in cancer cells, and these cells are considered to be mortal. Comparing the expression profiles between normal and cancer tissues with telomerase activity, we explored the genes specifically responsible for the immortalization of endometrial carcinoma cells.

   **Methods:** 1) DNAs and RNAs were extracted from cancerous and precancerous lesions as well as normal tissues in endometrium and subjected to Southern blotting analysis for terminal restriction fragment (TRF) lengths and real-time RT-PCR for the genes selected as candidates responsible for cellular immortalization of various cancer cells. 2) The genes specifically responsible for cellular immortalization of endometrial carcinomas are explored by using oligonucleotide microarrays, to develop a endometrial carcinoma-specific molecular target therapy in future.

   **Results and discussion:** Whereas most of the genes selected as candidates responsible for cellular immortalization of various cancers showed similar expression changes, some were differently expressed. Some other genes showed no significant differences in the expression levels between normal and cancerous tissues, but related to the pathological stages and/or patient prognosis. These genes were considered to be involved in tumor progression or immortalization rather than carcinogenesis.

3) **Telomere 3’-overhang and chemosensitivity to anticancer drugs**

   Nishimura, Y., Hiyama, K., Tanimoto, K., Nishiyama, M.
Purpose: The gene expression profiles alone are insufficient to explain the chemosensitivity to anticancer drugs in some cancer cell lines. To predict the chemosensitivity before treatment with anticancer drugs, we investigated relationship between chemosensitivity and telomere 3'-overhang which concerns with chromosome stability.

Methods: The lengths of telomere 3'-overhang were measured by T-OLA (telomere oligonucleotide ligation assay) in various human cancer cell lines. Chemosensitivity to anticancer drugs were evaluated by conventional MTT assay. The relationship between them was statistically analyzed. Then, we explored the genes differentially expressed between the cell lines with short and long telomere 3'-overhang. By transfecting the POT1-expressing vector to esophageal cancer cell lines, we established several clones with shortened telomere 3'-overhan as well as clones with elongated/shortened telomeres. We analyzed chemosensitivity of these clones.

Results and discussion: Although no significant correlation was observed between the length of 3'-overhang and sensitivity to anticancer drugs, some cancer cell lines with short telomere 3'-overhang showed relatively high resistance to several anticancer drugs. In esophageal cancer cells with shortened 3'-overhang due to overexpression of POT1, tendency of reduced chemosensitivity to 5-FU and paclitaxel was observed. Change in telomere length did not affect on the chemosensitivity. Thus, critical shortening of 3'-overhang may be related with chemoresistance.

4) Genes responsible for cellular immortalization common in various human cancers

Hiyama, K., Tanimoto, K., Tsugabe, M., Nishimura, Y., Nishiyama, M.

Purpose: Expression of telomerase is considered to be essential for attainment of immortality in almost all cancer cells, while it is often insufficient to immortalize normal somatic cells. To develop new anti-cancer strategy with high specificity, we searched for novel molecular targets that regulate cancer-specific immortalization.

Methods: 1) Using cDNA microarrays and oligonucleotide arrays, expression profiles are compared between before and after telomerase transfection in human fibroblasts and endothels. 2) Establishing various elongated-lifespan/immortal human cells by transfection of telomerase and transformed cells by transfection of SV40, expression profiles are compared between mortal normal, immortalized normal, mortal transformed, and immortal transformed cells. 3) Telomerase activity levels and expression profiles are also compared between normal cultured cells and cancer-derived cell lines. 4) Comparing 1)-3) data, we identified the genes commonly and specifically expressed in various immortal cancer cells. 5) Among the identified genes, effects of cellular growth by transfecting siRNAs of overexpressed genes and expression constructs of repressed genes into cancer cell lines were investigated.

Results and discussion: 1) During cellular immortalization, 18 and 20 genes were continuously dysregulated in fibroblasts and endothelial cells, respectively. Interestingly no gene was common for both cell types, and the expression levels were different from those reported in cancer cells. These findings indicate that genes involved in cellular immortalization in normal human somatic cells are unique according to the cell types and quite different from those in cancer cells. 2) Investigating the expression profiles of telomerase gene transfected mortal cells, immortalized transformed cells, established cancer cell lines derived from human cancers, and cultured normal somatic cells by using oligonucleotide arrays, commonly dysregulated genes and cancer-specific genes associated with cellular immortalization were obtained. We are now preparing to apply patent for the overexpressing genes whose siRNAs showed inhibitory effects on cellular proliferation. For the repressed genes, we found that its overexpression caused growth inhibition only in immortal transformed cells but not in immortal normal cells. Thus we expect this gene as a cancer-specific immortalization-suppressing gene.

5) Pancreatic cancer

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

Purpose: Pancreatic cancer shows poorest prognosis among solid tumors, and present chemotherapy is considered to be
not effective. Then, we tried to find the new molecular targets for pancreatic cancers.

**Methods:** By oligonucleotide microarray analysis using 10 pancreatic cancer cell lines and 10 pairs of pancreatic cancer and adjacent normal tissues, commonly overexpressing genes in cancer tissues and cell lines were selected.

**Results and discussion:** We detected 66 genes commonly expressed in pancreatic cancer tissues and cell lines, and further selected 15 genes by RT-PCR. Among them, 3 genes that have not been restricted by patent were subjected to functional evaluation on cellular growth of pancreatic cancer cell lines by transfection of antisense vector. Suppression of these genes showed inhibitory effects on cellular growth and these genes have potential to become the novel molecular targets for anticancer therapy for pancreatic cancer.

3. Molecular mechanisms of hypoxic response in solid tumors

**Background and Purpose:** Since homeostasis of oxygen supply is the most important for life, hypoxic responses are maintained strictly at the molecular levels. Recently, it is getting clearer that these hypoxic response systems are related to the development and progression of some diseases including solid tumors. Especially, hypoxia-inducible factor-1 (HIF-1), which is a transcription factor activated under hypoxia, is thought to be a key regulator of those responses. In our projects, we are trying to clarify the role of HIF-1-mediated signaling pathway in solid tumors to develop the molecular targeted therapies.

1) Transgenic mice of the human hypoxia-inducible factor-1α gene

Tanimoto, K., Nakamura, H., Hiyama, K., Nishiyama, M.

**Purpose:** Previously, we found the two variant forms of HIF-1α gene encoded its protein that had elevated transactivation capacity. To evaluate a role of genetic alterations of HIF-1α in solid tumors, we generated transgenic (tg) mice of wild- or mutant-type of HIF-1α gene.

**Methods and Results:** We have generated three types of tg mice which had WT, P582S or A588T of FLAG tagged HIF-1α gene, and several lines of F1-F8 generations were confirmed in each type of HIF-1α gene by PCR. We have also confirmed their expression of transgene and HIF-target genes by real-time RT-PCR and found that significant expression of human HIF-1α in stomach, small intestine, kidney, spleen, uterus, skin of tg mice. Especially, we found highest expression in spleen along with splenomas. Progression of these diseases is now being followed up.

2) Transcriptional regulation of the mismatch repair gene hMLH1 under hypoxic conditions

Tanimoto, K., Nakamura, H., Yunokawa, M., Hiyama, K., Nishiyama, M.

**Purpose:** Inactivation of the DNA mismatch repair (MMR) system induces genome instability, a cause of carcinogenesis and cancer progression. Hypoxia is known to induce genome instability, and has recently been shown to inactivate the MMR system via alteration of hMLH1 expression under hypoxic conditions. Here, we attempted to clarify the role of hypoxia-inducible transcription factors in regulation of hMLH1 expression.

**Methods and Results:** First, we evaluated expression levels of hMLH1 in HepG2 and MCF-7 cells in various periods of hypoxia by real-time RT-PCR: we found time-dependent down-regulation of hMLH1 expression as well as up-regulation of known hypoxia-inducible genes. To clarify the detailed mechanisms of down-regulation of hMLH1 expression, a 1649 bp length of the 5’ region of hMLH1 was subcloned. We tested a possible factor, bHLH family transcription factor, DEC1/2. We tried to clarify the role of DEC1/2, bHLH family transcription factor, in down-regulation of hMLH1 expression: A transient co-transfection experiment demonstrated repression of hMLH1 transcription by both DEC1 and 2 via their HDAC-dependent activities. Using a series of deletion mutants and HRE-mutants, two possible functional DEC1/2 responsive elements, E-box, were identified in the region from -273 to -4 of hMLH1. We finally confirmed the hypoxia-dependent up-regulation of DEC1 and DEC2, showing the reverse correlation to hMLH1 expression but not hMLH1 expression, which
suggested a mechanism for the down-regulation. The biological significance of DEC1/2 in hMLH1 regulation and MMR system are now being investigation.

3) Molecular mechanisms of resistance to chemotherapy and irradiation in oral cancer cells under hypoxic conditions

Nakamura, H., Tanimoto, K., Yunokawa, M., Hiyama, K., Nishiyama, M.

**Purpose:** Hypoxic cancer cells are known to show biologically aggressive phenotypes, such as therapeutic resistances. Hypoxia-inducible factor-1α (HIF-1α), the key transcription factor under hypoxia, controls a variety of genes resulting in these malignant phenotypes, but the functional mechanisms of HIF-1α and hypoxia-related genes in oral squamous cell carcinomas (OSCC) remain unclear. To develop a novel strategy against resistance to anti-cancer therapies such as chemotherapies and irradiations, we are trying to clarify the molecular mechanisms.

**Methods and Results:** We first compared protein expression levels of HIF-1α in OSCC cell lines (HSC-2, HSC-3, HSC-4, KOS-2, Ca9-22, KB). The immunoblotting revealed that hypoxic treatment (1% pO₂ for 8 hours) drastically increased HIF-1α protein in 5 cell lines, although it was hardly detectable in Ca9-22. Hypoxic responses of these cell lines were evaluated by using luciferase reporter-including hypoxia response element. Transient transfections with the reporter demonstrated that hypoxia induced reporter activity, the highest in HSC-2 and the lowest in Ca9-22, thus we used these two cell lines in next experiments. We evaluated the sensitivities of both cell lines to CDDP treatments under normoxia (21% pO₂) and hypoxia (1% pO₂) by MTT assay. Interestingly, 24- or 48-hour continuous exposure as well as pre-treatment of hypoxia for 24 hours conferred CDDP-resistance in HSC-2 but did not in Ca9-22. Hypoxia-inducible genes were analyzed in both cell lines by using CodeLink™ Expression Bioarray System, UniSet Human 20K I Bioarray (1981 probes). The comprehensive gene expression analyses demonstrated that 24-hour hypoxic treatment up-regulated 2638 and 1173 genes, and down-regulated 2881 and 2404 genes in HSC-2 and Ca9-22, respectively. Among them, 2130 genes were specifically up-regulated in HSC-2, while 2332 genes were down-regulated. We found that they included genes which are well known as sensitivity determinants of CDDP, such as VEGF, HSPB, IL6, MLH1, and MSH2. These results suggest that our selected genes may play some important roles in hypoxia-induced CDDP-resistance. Functional analyses of these novel hypoxia-inducible genes are now going on.

4) Transcriptional protein complexes of HIF-1

Tanimoto, K., Nakamura, H., Hiyama, K., Nishiyama, M.

**Purpose:** To develop the HIF-1-targeted therapies for various diseases, we are trying to identify the activators or repressors of HIF-1 protein.

**Methods and Results:** To develop the HIF-1-targeted therapies for various diseases, we are trying to identify the activators or repressors of HIF-1 protein.

**Methods and Results:** To purify the DNA-binding forms of HIF-1 complexes, plasmid vector containing three tandem repeated hypoxia-response element (3xHRE) was constructed. The 3xHRE was amplified with biotinylated T7 primer and T3 primer, and purified. The DNA-binding forms of HIF-1 complexes were purified from nuclear extracts of hypoxic HepG2 or HSC-2 and confirmed by immunoblotting for anti-HIF-1α. Detailed optimizations are on-going now.

List of contributions

A. Original Papers

1. Hiyama, K., Otani, K.¹, Ohtaki M.¹, Satoh K.¹, Kumazaki, T.¹, Takahashi, T.¹, Mitsui, Y.², Okazaki, Y.², Hayashizaki, Y.², Omatsu, H.², Noguchi, T., Tanimoto, K., Nishiyama, M. (¹Dept. Environmetr. Biometr., ²Jpn


B. Meeting Presentations


33. Hiyama, K., Noguchi, T., Tanimoto, K., Nishiyama, M.: Commonly and specifically dysregulated gene in various


35. Tanimoto K., Hiyama K., Nishiyama M.: Transcriptional regulation of the human mismatch repair gene, MLH1 under hypoxic conditions. 9th Annual Meeting of Jpn Soc. of Mol. Target Ther., Kyoto, 2005. 7. (In Jpn) (G)


63. Fujiwara, S.*¹, Noguchi, T.*¹, Takeno, S.*¹, Kimura, Y.*¹, Fumoto, S., Anami, K.*¹, Noguchi, T.*¹, Harada, K.*¹, Shibata, T.*¹, Kawahara, K.*¹ (*2nd Dept. Surg., Oita Univ.): Hypermethylation of p16 promoter in esophageal squamous cell carcinoma. 106th Annual Meeting of Jpn Surg. Soc., Tokyo, 2006. 3. (In Jpn)


C. Others


(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.