Sprawozdania

Chemoprevention, Cell Adhesion, and Apoptosis: Report from the 87th Annual Meeting of the American Association for Cancer Research

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This paper discusses some of the results and opinions presented to the 87th Annual Meeting of the American Association for Cancer Research in Washington D.C., USA. The authors do not neccessarily agree with all the statements, nor should the reader accept them as absolutely true. Since understanding of tumorigenesis is a long-term process requiring both innovative ideas and critical feedback, controversial issues are also included in this report. A total of 4200 papers from 7800 authors were presented. Although Polish scientists were well represented at the meeting, only 6 came from Polish academic institutions. For comparison, 182 scientists represented Germany. As is traditional, Ex-

perimental Therapeutics had the largest number of presentations, 1072, followed by Molecular Biology and Biochemistry with 764 presentations, Cellular Biology with 669 presentations, Carcinogens with 457 presentations, Clinical Trials with 338 presentations, and Immunology with 335 presentations. Obviously, the authors were unable to cover all sessions in this report and are truly sorry if some important aspects of cancer research have been omitted.

The Presidential Address, delivered by Dr. Bertino, described recent findings relating to the resistance of cancer cells with structural defects of a number of genes involved in the regulation of the normal cell cycle to radio- and chemotherapy. A loss of function by p53 gene and amplification of Bcl-2 gene were major mechanisms (1).

Chemoprevention was one of the most extensively discussed issues at the meeting. Currently, there is almost universal agreement that cancer is a disease that is best dealt with by prevention. Chemoprevention is designed specifically to inhibit multistep and field tumorigenesis (2). Chemopreventive agents can be classified according to different criteria such as the mechanism of action or target. For example, the first class of chemopreventive agents comprises blockers of the interaction between electrophilic moieties and target sites in a cell. The second class acts by decreasing the sensitivity of vulnerable target tissues to carcinogens e.g., complex hormonal protection of mammary gland during pregnancy (3). The third class of drugs called suppressing agents is targeted to influence tumorigenesis-related events such as initiation, promotion, mutations, DNA amplification, translocation, etc. This class comprises retinoids, hormone antagonists, modulators of hormone metabolism, nonsteroidal antiinflammatory drugs such as aspirin and sulindac, difluoromethylornithine, calcium, vitamin D3, and organoselenium compounds (4-7).

A number of reports were focused on a search for new sources of anticancer agents in natural products such as black tea, green tea, garlic, and citrus (8-10). For some participants, this signaled a coming crisis in cancer research; however, to others this showed that scientifically-oriented western society is rediscovering forgotten ideas from the past. Indeed, the idea of chemoprevention originated in the early 1920's when chemical carcinogens were first described together with inhibition of their action by antagonists. These early findings met serious criticism and disbelief, until a major breakthrough in 1970's demonstrated that phenolic antioxidants, widely used as dietary preservatives, protected rodents against tumors in different organs (11-12). There is a consensus that vegetables and fruits lower the risk of cancer (13); however, paradoxically, diet remains one of the major factors causing cancer (14). Most carcinogens present in the environment are innocuous unless activated enzymatically during a process called procarcinogen activation by Phase I enzymes such as hepatic cytochromes P-450 1A2, 2E1, 3A4 and extrahepatic cytochrome P-450 1A1 (15). During the meeting, an additional cytochrome P-450 1B1 was reported (16) by Dr. Guengerich of the Department of Biochemistry, Vanderbilt University School of Medicine in Nashville to be expressed constitutively in breast, lung, prostate, uterus and a

number of fetal tissues. Since expression of this enzyme was found to be induced by a procarcinogen, 2,3,7,8-tetrachlorodibenzo-p-dioxin, a suggestion was made that its activity in extrahepatic tissues may contribute to tumorigenesis. The cytochrome P-450 1B1 activates 11,12-dihydroxy-11,12-dihydrodibenzo[α, l]pyrene, 1,2-dihydroxy-1,2-dihydro-5-methylchrysene, (+)-7,8-dihydroxy-7,8-dihydrobenzo[α]pyrene, 3,4-dihydroxy-3,4-dihydrobenzo[c]phenanthrene, 3-amino-1,4-dimethyl-5H-pyrido[4,3-β]-indole (Trp-P-1), 2-aminoanthracene, 3-methoxy-4-aminoazobenzene, and 2-nitropyrene. On the other hand, many eucaryotic cell types possess xenobiotic metabolizing enzymes, i.e., Phase 2 enzymes such as quinone reductase or glutathione transferase. It is believed that the Phase 2 enzymes protect cells against products of the Phase I enzymes. The activated carcinogen becomes a substrate for the Phase II enzymes and is removed from cells during a process called detoxication. A balance between activities of these two classes of enzymes seems to contribute to the outcome of exposure to carcinogens. Expression of Phase 2 enzymes can be induced by a number of agents. Dr. Talalay of the Department of Pharmacology and Molecular Sciences, The John Hopkins University School of Medicine in Baltimore summarized his research on Phase 2 inducers among edible plants such as the family Crucifera and the genus Brasicca which includes broccoli, brussels sprouts, cabbage, and cauliflower. First, his team developed an assay to measure a typical and representative Phase 2 enzyme, NAD(P)H:quinone reductase, in murine hepatoma cells. Subsequently, they selected a number of species particularly rich in inducer activity. After isolation of sulforaphane as the principal and very potent Phase 2 enzyme inducer from a broccoli species (17), they demonstrated that this compound and its synthetic analogs inhibited mammary tumorigenesis in rats (18). Mechanisms of induction of Phase 2 enzymes were presented at the meeting by a research team from the Schering-Plough Research Institute in Kenilworth. Transcriptional activation of both glutathione S-transferase gene and quinone reductase gene is mediated by at least 2 cis-acting regulatory elements, XRE and ARE, present in the 5'-flanking region of the genes (19). Moreover, activation of glutathione S-transferase-Ya subunit gene through the ARE in response to oxidative stress is mediated via a unique signal transduction pathway and not directly by members of AP-1 family. This finding also suggests a target for a new family of drugs. Nonetheless, three facts must be kept in mind. First, it is known which carcinogens may induce a given type of tumor; however, its etiology cannot be determined easily in an individual case. Also, tumorigenesis can occur in the absence of exposure to carcinogens. Secondly, glutathione S-transferases can activate some of the procarcinogens instead of the expected inactivation (20). Finally, clearance of a toxic agent is a constitutive reaction which removes majority of the agent outside the cells. Although pharmacologic induction of Phase 2 enzymes may fascilitate this clearance, it may not protect cellular genome against carcinogens.

A very interesting, well-illustrated, and technically difficult work presented by Dr. Dębiec-Rychter of the Department of Oncology, University Medical

School in Łódź, Poland focused on a study of tissue-specific expression of human N-acetyltransferase 1 and 2 detected by non-isotopic *in situ* hybridization. These enzymes are likely to be involved in activation of exogenous carcinogenic amines as well as in the metabolism of endogenous arylalkylamines important as neurotransmitters. The mRNAs were detected in a number of human tissues including intestine, bladder, kidney, mammary gland, and cerebral cortex (21).

Sessions concerning molecular mechanisms of retinoid action or applications of retinoids in cancer treatment were very well attended during the meeting. In the Dewitt S. Goodman Lecture, Dr. Mangelsdorf of the Department of Pharmacology, Howard Hughes Medical Institute in Dallas summarized his experience with retinoid X receptors. Besides classic subfamilies of retinoic acid receptors and retinoid X receptors, he described a novel class of orphan receptors including a recently cloned hLXR. Due to multiple interactions with the other members of the steroid/retinoid receptor gene superfamily, hRXRs are key regulators of nuclear hormone receptor signaling (22).

Retinoids have been successfully applied in therapy of a number of human malignancies (2). Results of breast cancer chemoprevention with 4-HPR and tamoxifen were discussed by Dr. Veronesi of the National Cancer Institute in Milan, Italy. This study started in March 1987 and was designed to prevent contralateral breast cancer in women with previous stage 1 breast carcinoma. The cohort of 2,972 women was known to have a good prognosis and a constant risk of contralateral tumor (0.8%/year) (23). 4-HPR was given *per os* during a randomized trial in a dose of 200 mg/day for 5 years versus placebo. Although the actual sample size had only 87% of the statistical power of the ideal cohort, the results pointed out a preventive effect of the drug in premenopausal women. In addition, data suggested that 4-HPR can protect premenopausal women against ovarian cancer. Toxicity consisted mainly of diminished adaptation to darkness, eye dryness, and mild dermatologic disorders. The treatment influenced the amounts of IGF-1 in blood plasma in premenopausal women with breast cancer suggesting its role as a surrogate endpoint biomarker (24). While the interaction with menopausal status supports the concept of a complex interference by the retinoid with the estrogen signal transduction pathway, Dr. Veronesi speculated that 4-HPR may act in women with genetic susceptibility to breast cancer, since they are mostly premenopausal and show highest incidence of bilaterality and a high frequency of ovarian cancer.

Chemopreventive trials with retinoids were also initiated in bladder cancer patients, where little was known about the molecular mechanisms of retinoid action in uroepithelial cells. The authors of this report presented results of their work on sex steroid and retinoid signaling and expression of retinoid-responsive genes in uroepithelial cells. The presentation at the AACR meeting in Toronto in 1995, awarded a first prize for the session by the Scientific Committee, identified a number of key elements involved in retinoid signal transduction in this cell type (25). This time, an *in vitro* model comprising

8 cell lines (2 immortalized by SV-40 virus and 6 bladder carcinoma-derived cell lines) was tested as to the sensitivity to all-trans retinoic acid, 13-cis retinoic acid, and a synthetic retinoid, 4-HPR. Surprisingly, cell lines that were sensitive to 4-HPR were not sensitive to the other retinoids. Only one, a transitional cell papilloma-derived cell line, RT-4, remained insensitive to all retinoids tested. Unlike transitional cell carcinoma-derived lines, RT-4 cells do not express some retinoid-responsive genes, i.e., CRBP I, CRABP I, ICAM-I, MK cytokine, and transglutaminase. This difference suggests that variable molecular pathways are active during uroepithelial tumorigenesis. A molecular study of expression of 12 retinoid-responsive genes by Relative RT-PCR demonstrated that cells which were sensitive to 4-HPR expressed either no CRABP I mRNA, or very low amount of this mRNA, or was strongly down-regulated by retinoid treatment. Since CRABP I protein is considered to be an intracellular regulator of retinoid activity, a hypothesis was developed that 4-HPR binds to the same receptor proteins as all-trans retinoic acid but with a higher afinity. Indeed, it was observed that expression of two retinoid-responsive genes, hRARa and transglutaminase, was significantly increased by 4-HPR as compared to control and all-trans retinoic acid-treated cells. Moreover, it was demonstrated that there were multiple patterns of gene expression associated with resistance or sensitivity to retinoids. Thus, only CRABP I mRNA was identified as a potential biomarker for retinoid sensitivity. Its specificity, sensitivity, and predictive value remain to be determined (26). Growth suppression and induction of apoptosis in human uroepithelial cells by 4-HPR were reported by Dr. Liebert of University of Texas M. D. Anderson Cancer Center in Houston (27). Recent findings point out that an enzyme, transglutaminase, which catalyzes a reaction of an acyl transfer between peptide-bound glutamyl moieties and various primary amines, can be a marker of differentiation and apoptosis. Transglutaminase gene contains retinoid responsive element within its promoter and is up-regulated by retinoids (28). Interestingly, the activity of the enzyme was lower in malignant tissues, but higher in metastases as compared to normal-appearing tissues (29). Although biological significance of this phenomenon is not clear, the enzyme may be useful in evaluation of chemopreventive action of retinoids in transformed uroepithelial cells.

Dr. Greider from the Cold Spring Harbor Laboratory summarized the state of the art in telomeres and telomerase research during the Cornelius P. Rhoads Memorial Award Lecture. A link between telomeres, short nucleotide repeats, and tumor progression has become evident in the last few years (30). Telomeric DNA contains tandemly repeated G-rich sequences which vary in regard to the sequence among species. DNA polymerases require RNA as a primer and polymerize only in the 5' to 3' direction. Therefore, chromosomes cannot be fully copied at their ends and would shorten after each cellular division eventually leading to cell death. Telomere length is regulated in such manner that the repeats are continually added onto chromosome ends (31). Telomerase is a ribonucleoprotein DNA polymerase that elongates telomeres. The presence of telomerase activity in a number of

human malignancies and lack of this activity in normal-appearing tissues adjacent to the tumor suggest that this enzyme is required by transformed cells for sustained growth, and therefore it could be a target for antitelomerase therapy (32). It is hypothesized that other genes suppress telomerase activity and their identification is the most crucial objective of the telomerase research.

Dr. Korsmeyer led a Meet-the-Expert Sunrise Session to discuss Apoptosis: regulation and oncogenesis. In spite of the early hour, many enthusiastic researchers appeared at this seminar, since apoptosis was an issue of general interest at this year's meeting. The Bcl 2 gene was identified as a gene involved in blocking programmed cell death rather than promoting proliferation (33). This gene is particularly well expressed in embryonal tissues. Dr. Korsmeyer found that transgenic mice that overexpress Bcl 2 gene in the B cell lineage have extended cell survival and progress to high grade lymphomas. On the other hand, Bcl 2 deficient mice complete embryonal development sooner and undergo fulminant lymphoid apoptosis of thymus and spleen. A second gene, Bax, counters Bcl 2 and promotes apoptosis, while a third gene, Bad, heterodimerizes with Bcl 2 molecules and restores apoptosis (34). In conclusion, susceptibility to a death stimulus in a cell is determined by a complex set point influenced by interactions between these family members (35-37).

Cell adhesion, signal transduction, and integrins were topics of great interest at the meeting. Integrins are a family of cell-surface receptors that are involved in a number of cellular functions such as cell-cell and cell-matrix adhesion, lymphocyte trafficking, cell motility, homeostasis, and inflammation (38,39). Integrins transduce signals regulating gene expression and differentiation (40). In addition, evidence suggests that integrin signaling and Ras signaling are linked. Moreover, integrin signaling activates a set of early response genes including a number of cytokines. This occurs due to the activation of Syk tyrosine kinase and the Nf-kB transcription factor. Other studies pointed out that integrins and some oncogenes have antagonistic effects on proliferation and differentiation of cells (41).

Surgery remains the initial method of management of colorectal cancer patients. Some progress has been achieved to minimize recurrence and metastasis with postoperative adjuvant chemo- and radiotherapy; however, the only agent among approximately 50 cytostatics tested effective against colorectal carcinoma-derived cells was 5-fluorouracil (42). Although this cytostatic normally has a relatively low number of side effects, an unexpected severe toxicity, neutropenia, thrombopenia, and neurological damage can occur frequently. Patients receiving the agent had lower activities of dihydropyrimidine dehydrogenase, an enzyme responsible for 5-fluorouracil metabolism, than was found in the control population. A gene encoding this enzyme was recently cloned, sequenced, and found to be mutated in patients exhibiting inherited thymine-uraciluria. The mutant mRNA was missing 165 nucleotides corresponding to one exon. Isolation of the gene from a YAC library enabled sequencing and identification of its intron and exon struc-

ture. Patients susceptible to developing severe toxic reactions to 5-fluorouracil can now be identified a priori. Dr. Dzięgielewski and Dr. Konopa of the Department of Pharmaceutical Technology and Biochemistry, Technical University in Gdańsk presented results of their study on imidazoacridinones, a new class of cytostatics developed in Poland. According to their data, these compounds exhibit particularly strong antitumor effect in colorectal carcinomas (43). Imidazoacridinones intercalate with DNA and inhibit topoisomerase II. These agents possess a side chain diaminoalkiloamino residue that appears to be crucial for biological activity of the agents. One of the derivatives, C-1311, is currently being involved in a Phase I clinical study in England. Hopefully, the new class of drugs will soon enrich the poor arsenal of cytostatics that are active in colorectal cancer patients.

Although gene therapy of colorectal carcinoma remains more theoretical than practical, efforts to make gene transfer into the malignant cells specific, effective, and safe are in the focus of interest. Dr. Bielińska and Dr. Kukowska-Latałło of the University of Michigan in Ann Arbor designed vectors offering a possibility of colonocyte-specific gene transfection. They constructed mammalian expression vectors with a minimal CEA promoter which has been cloned upstream of the beta-galactosidase gene or a herpes simplex virus thymidine kinase gene. Since this latter construct achieved only up to 30% of activity as compared to the control vectors, an enhancer from the immediate early gene of CMV was inserted at the 5' of the CEA promoter. The improved version of the vector achieved 180% of activity in CEA-producing colon cancer cell lines and, in addition, the cell lines transfected with the improved construct became more sensitive to gancyclovir therapy than controls (44).

Mechanisms of metastasis formation remain understudied from the molecular biological perspective. The increased number of research projects concerning this issue should provide more information. Dr. Waliszewski presented results of experiments performed in the Department of Cancer Biology, The Cleveland Clinic Foundation in co-operation with Dr. Hassel, concerning investigation of interferon alpha-induced genes in colorectal carcinoma-derived cells. The generalized resistance of colon carcinoma-derived cells matched clinical resistance of colon cancer to this cytokine (45). Although no antiproliferative effect was observed, genes involved in interferon signal transduction were induced in the majority of cell lines studied (46); however, resistance was not associated with a single pattern of expression of interferon-responsive genes. Expression of two genes, IRF-1 and RNase L, involved in the response to interferon alpha treatment in human eucaryotic cells was altered (47,48). IRF-1 was expressed constitutively at very low amounts, and RNase L was expressed relatively abundantly. However, interferon alpha did not induce either gene. Furthermore, one of the cell lines, SW 620, derived from colorectal carcinoma lymph node metastasis, was identified as the first human cell line to be deficient in both genes. In addition, RNase L gene was not expressed in a number of surgical specimens of liver metastases of colorectal carcinoma, but was present in metastases

derived from prostate cancer. Transfection confirmed that the gene does modify cellular morphology and proliferation rate; however, no significant changes of tumor growth were observed after injection into nude mice. These findings suggest that alterations in the RNase L gene, and, most likely, IRF-1 gene are involved in molecular mechanisms leading to the resistance to interferon alpha and formation of metastases of colorectal carcinoma (49). Dr. Fujita from the Department of Surgery, National Cancer Center Hospital in Tokyo, Japan reported that using enriched PCR-SSCP it was possible to detect micrometastases of colorectal carcinoma in tissue adjacent to malignant lesions. Moreover, he found that the mutation rate in ki-ras codon 12 in normal-appearing liver tissue was much higher than in liver tissue of non-cancer patients (50). An elegant clinical study, awarded a prize by the Scientific Committee, concerning prognosis assesment of chemotherapeutically-treated colorectal liver metastases was presented by Dr. Mohler from the German Cancer Research Center in Heidelberg, Germany. ^{18}F-5-Fluorouracil kinetics in the metastases were measured by positron emission tomography and correlated with growth rates. 14 patients with proven metastases received a standard Folinic Acid/5-Fluorouracil therapy and, based upon results of positron emission tomography and calculated standardized uptake volume, were classified into two subgroups. The subgroup with standardized uptake volume higher than 2.8 was found to have statistically better prognosis than the other subgroup (51).

Progress in the biology of neuroblastoma was summarized by Dr. Brodeur from the Childrens Hospital of Philadelphia. The most frequent genetic changes in this malignancy include the deletion of the short arm of chromosome 1p, suggesting, in his opinion, a tumor suppressor gene locus (52). Furthermore, high expression of the trk-A and trk-C oncogenes is associated with a favorable outcome (53). A poor outcome is associated with amplification of n-myc protooncogene (54). Based upon the genetic abnormalities, patients with neuroblastomas were stratified into three biological subsets. The first subset comprised those with a high expression of trk-A oncogene, no n-myc amplification or deletion of 1p chromosome. This subset of patients had a very good prognosis and low stage disease usually. The second subset of patients had tumors expressing low amounts of trk-A and trk-C oncogenes and also the lack of n-myc oncogene amplification; however, they could have deletion of chromosome 1p or other structural defects. While the general outcome was rather poor, the tumors initially responded to the therapy, and patients could survive for several years. The third subset of patients with poor prognosis had tumors amplifying n-myc oncogene and having deletion of chromosome 1p, and expressing no trk oncogene; however, recent protocols for neuroblastoma treatment incorporating myeloablative regimens with autologous purged bone marrow transplantation have demonstrated that a subset of children with stage IV high-risk neuroblastoma can be long term survivors (55). The improvements in the therapy also include eradication of multidrug resistance by agents with low hematopoietic toxicity such as 13-cis retinoic acid and inhibitors of ribonucleotide reductase such as the iron

chelator deferoxamine (56-58). Dr. Dębiński from the Milton Hershey Medical Center reported studies identifying the interleukin 13 receptor as a new target for the treatment of human gliomas using chimeric toxic proteins composed of human interleukin 13 and a derivative of *Pseudomonas exotoxin* PE38QQR (59). Dr. Wiranowska from the Department of Anatomy, University of South Florida reported on inhibition of glioma invasiveness *in vitro* following interferon alpha treatment (60).

A team from the Department of Thoracic Surgery, University Medical School in Bialystok, Poland reported multivariate analysis of a soluble fragment of cytokeratin 19, CYFRA 21-1 in serum samples of 75 patients with operable squamous cell lung cancer (stages I-IIIa) demonstrated increased amounts of CYFRA 21-1 which was associated with higher risk of recurrence (61).

Free exchange of ideas represents one of the major benefits offered by the AACR meeting to scientists and the scientific community. The leading figures in cancer research present their results and lively, sometimes controversial, discussions often occur with usually large audiences. The discussions reveal that some of the concepts and findings published in the top peer-reviewed journals are not nearly so well accepted as might be thought based upon the name and rank of the journal. Unfortunately, the published literature tends to be dominated by the so-called solid papers documenting detail in almost excruciating thoroughness and innovative papers with new ideas are stifled by the gauntlet of conservatism (62). This issue is particularly important for young investigators. Cancer research seems to be dominated by the trend of the year, probably because it is starving for the new ideas kept off the stage by self-interest and overly rigorous demands for proof. However, at the AACR, the policy of allowing each member a paper with only minimal review guarantees the full range of ideas have an opportunity for discussion, thereby adding a dimension to this meeting that cannot be duplicated by reading the literature.

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References

1. Li W. W., Fan J., Hochhauser D., Banerjee D., Zielinski Z., Almasan A., Yin Y., Kelly R., Wahl G. M., Bertino J. R., (1995), Proc. Natl. Acad. Sci. USA, 92, 10436-10440.
2. Greenwald P., Kelloff G., Whitman-Burch C., Kramer B., (1995), CA Cancer J. Clin., 45, 31-49.
3. Russo J., Russo I. H., (1994), Cancer Epidemiology, Biomarkers, Prevention, 3, 353-354.
4. El-Bayoumy K., Upadhyaya P., Chae Y., Sohn O., Rao C.V., Fiala E., Reddy B., (1995), J. Cell Biochem., 22, 92-100.
5. Lipkin M., Newmark H., (1995), J. Cell Biochem., 22, 65-73.
6. Lipman S., Heyman R., Kurie J., Benner S., Hong K., (1995), J. Cell Biochem., 22, 1-10.
7. Meyskens F., Gerner E., (1995), J. Cell Biochem., 22, 126-131.
8. Xu M., Bailey A. C., Hernaez J., Taoka C., Dashwood R. H., (1996), Proc AACR, 37, 265.

9. Wang Z. Y., Huang M. T., Lou Y. R., Xie J. G., Reuhl K. R., Newmark H. L., Ho C. T., Yang C. S., Conney A. H., (1994), Cancer Res., 54, 3428-3435.
10. Luyengi L., Lee I.S., Mar W., Fong H. H. S., Pezzuto J. M., Kinghorn A. D., (1994), Phytochemistry, 36, 1523-1526.
11. Wattenberg L. W., (1992), Cancer Res., 52, 2085-2091.
12. Wattenberg L. W., (1993), Cancer Res., 53, 5890-5896.
13. Block G., Patterson B., Subar A., (1992), Nutrition and Cancer, 18, 1-29.
14. Doll R., (1992), Cancer Res., 52, 2024-2029.
15. Guengerich F. P., Shimada T., (1991), Chem. Res. Toxicol., 4, 391-407.
16. Sutter T. R., Tang Y. M., Hayes C. L., Wo Y. Y. P., Jabs E. W., Li X., Yin H., Cody C. W., Greenlee W. F., (1994), J. Biol. Chem., 269, 13092-13099.
17. Zhang Y., Talalay P., Cho C. G., Posner G. H., (1992), Proc. Natl. Acad. Sci. USA, 89, 2399-2403.
18. Zhang Y., Kensler T. W., Cho C. G., Posner G. H., Talalay P., (1994), Proc. Natl. Acad. Sci. USA, 91, 3147-3150.
19. Rushmore T. H., Pickett C. B., (1993), J. Biol. Chem., 268, 11475-11478.
20. Thier R., Taylor J. B., Pemble S. E., Humphreys W. G., Persmark M., Ketterer B., Guengerich P., (1993), Proc. Acad. Sci. USA, 90, 8576-8580.
21. Dębiec-Rychter M., Land S. J., King Ch. M., (1996), Cancer Res., 56, 1517-1525.
22. Willy P. J., Umesono K., Ong E. S., Evans R. M., Heyman R. A., Mangelsdorf D. J., (1995), Genes Dev., 9, 1033-1045.
23. Veronesi U., de Palo G., Costa A., Formelli F., Marubini E., Del Vecchio M., (1992), Natl. Cancer Inst. Monog., 12, 93-97.
24. Torrisi R., Pensa F., Orengo M. A., Catsafados E., Ponzani P., Boccardo F., Costa A., Decensi A., (1993), Cancer Res., 53, 4769-4771.
25. Waliszewski P., Benbrook D., Nasim M., Hurst R. E., (1995), Proc. AACR, 36, 630.
26. Waliszewski P., Waliszewska M. K., Niekrasz M., Gordon A. N., Hemstreet G. P., Hurst R. E., (1996), Proc. AACR, 37, 233.
27. Liebert M., Grossman H. B., Lotan R., (1996), Proc. AACR, 37, 387.
28. Fraij B. M., Birckbichler P. J., Patterson M. K. Jr., (1995), J. Biol. Chem., 267, 22616-22623.
29. Aeschlimann D., Paulsson M., (1994), Thrombosis Homeostasis, 71, 402-415.
30. de Lange T., (1995), *Telomeres*, Eds. Blackburn E.H., Greider C.W., Cold Spring Harbor Laboratory Press, 265-293.
31. Prowse K. R., Greider C. W., (1995), Proc. Natl. Acad. Sci. USA, 92, 4818-4822.
32. Kim N. W., Piatyszek M., Prowse K. R., Harley C. B., West M. D., Ho P. L., Coviello G. M., Wright W. E., Weinrich S. L., Shay J. W., (1994), Science, 266, 2011-2014.
33. Chao D. T., Linette G. P., Boise L., White L. S., Thompson C. B., Korsmeyer S. J. (1995), J. Exp. Med., 182, 821-828.
34. Yang E., Zha J., Jockel J., Boise L. H., Thompson C. B., Korsmeyer S. J., (1995), Cell, 80, 285-291.
35. Korsmeyer S., (1995), Trends Genetics, 11, 101-105.
36. Korsmeyer S. J., Yin X. M., Oltvai Z. N. Veis-Novack D. J., Linette G. P., (1995), Bioch. Biophys. Acta, 1271, 63-66.
37. Linette G. P., Korsmeyer S. J., (1994), Current Opinion Cell Biol., 6, 809-815.
38. Ruoslahti E., Reed J. C., (1994), Cell, 77, 477-478.
39. Ruoslahti E., (1995), Invasion and Metastasis, 14, 87-97.
40. Rosales C., O'Brien V., Kornberg L., Juliano R., (1995), Biochem. Biophys. Acta, 1242, 77-98.
41. Lin T. H., Rosales C., Mondal K., Bolen J. B., Haskill S., Juliano R. L., (1995), J. Biol. Chem., 270, 16189-16197.
42. Waliszewski P., Waliszewski W., (1995), Gastroent Pol., 2(3), 243-247.
43. Dzięgielewski J., Konopa J., (1996), Proc. AACR, 37, 410.
44. Kurane S., Krauss J. C., Bielinska A. U., Kukowska-Latałło J. F., Cameron M. J., Baker J. R., Chang A. E., (1996), Proc. AACR, 37, 342.

45. Bukowski R., Inoshita G., Yalavarthi P., Murthy S., Gibson V., Budd G. T., Sergi J. S., Bauer L., Prestifilippo J., (1992), Cancer, 69, 889-892.
46. Williams B. R. G., (1991), J. Interferon Res., 11, 207-213.
47. Reis L. F. L., Harada H., Wolchok J. D., Taniguchi T., Vilcek J., (1992), EMBO J., 11, 185-193.
48. Hassel B. A., Zhou A., Sotomayor C., Maran A., Silverman R. H., (1993), EMBO J., 12, 3297-3304.
49. Waliszewski P., Hassel B., (1996), Proc. AACR, 37, 216.
50. Fujita S., Fukayama N., Nakashima Y., Moriya Y., Sugihara K., Akasu T., Sugano K., (1996), Proc. AACR, 37, 196.
51. Mohler M., Gutzler F., Dimitrakopoulou-Strauss A., Stremmel W., Strauss L., Rath U., (1996), Proc. AACR, 37, 202.
52. White P. S., Maris J. M., Beltinger C., Sulman E., Marshall H. N., Fujimori M., Kaufman B. A., Biegel J. A., Allen C., Hillard C., (1995), Proc. Natl. Acad. Sci. USA, 92, 5520-5524.
53. Yamashiro D. J., Nakagawara A., Ikegaki N., Liu X. G., Brodeur G. M., (1996), Oncogene, 12, 37-41.
54. Brodeur G. M., (1994), Sem. Diag. Pathol., 11, 118-125.
55. Stram D. O., Matthay K. K., O'Leary M., Reynolds C. P., Seeger R. C., (1994), Prog. Clin. Biol. Res., 385, 287-291.
56. Blatt J., (1994), Anticancer Res., 14, 2109-2112.
57. Hann H. W. L., Stahlhut M. W., Rubin R., Maddrey W. C., (1992), Cancer, 70, 2051-2056.
58. Villablanca J. G., Khan A., Avramis V., Seeger R. C., Matthay K. K., Ramsay N. K., Reynolds C. P., (1995), J. Clin. Oncology, 13, 894-901.
59. Dębinski W., Obiri N. I., Pastan I., Puri R. K., (1996), Proc. AACR, 37, 416.
60. Wiranowska M., Saporta S., (1996), Proc. AACR, 37, 457.
61. Niklinski J., Furman M., Chyczewski L., Chyczewska E., Laudański J., (1996), Proc. AACR, 37, 198.
62. Gleick J., (1987), *Chaos. Making a new science*, Penguin Books, New York.

Chemoprevention, Cell Adhesion, and Apoptosis: Report from the 87th Annual Meeting of the American Association for Cancer Research

Summary

The largest world forum for cancer research, the 87th Annual Meeting of American Association for Cancer Research, was held in Washington D. C., USA on April 20-24, 1996. This meeting was dominated by presentations on molecular mechanisms of chemoprevention, signal transduction, cell adhesion, cell cycle regulation, apoptosis, metastasis formation, and gene therapy. Tumor suppressor genes and oncogenes received much less attention than last year. The meeting celebrated the 25th Anniversary of the National Cancer Act presenting a number of clinically-oriented discoveries; however, some participants were less optimistic predicting a crisis in cancer research. Polish science was represented by a number of researchers mostly working abroad. Some of their achievements are discussed briefly in this report.

Key words:
cancer, chemoprevention, apoptosis, adhesion, RNase L, metastasis.

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