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Centre of Excellence

Division of Experimental Oncology

Department of Cancer Epidemiology
Department of Experimental and Clinical Radiobiology
Department of Medical Physics
Department of Molecular Biology
Department of Tumor Biology
and
Laboratory of Molecular Diagnostics and Functional Genomics
within Department of Nuclear Medicine and Oncological Endocrynology
Laboratory of Molecular Radiobiology
within Department of Radiotherapy

http://cd.io.gliwice.pl

Scientific Report 2007-2008

General Information. Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Branch in Gliwice, is an European Comprehensive Cancer Center and one of the largest clinical institutions in Poland. The Division of Experimental Oncology is involved in many aspects of basic, translational, and clinical research in oncology since 1950. Its research staff is well-trained, experienced and is well recognized on the Polish and international research maps. In 2004, the Division of Experimental Oncology was awarded the title of "National Center of Excellence" by the Polish Ministry of Science.

Research staff. The staff of the Center of Excellence numbers about 70 people with university education and includes: 8 full professors, 6 assistant professors and 27 Ph.D. researchers. The scientists are proficient in modern molecular and cell biology methods. Particularly strong areas of expertise are gene cloning, gene structure and function, transgenic mice, DNA microarrays, RT-PCR, immunohistochemistry, confocal microscopy, polymorphic genes involved in metabolism of xenobiotics and DNA repair. They have close and efficient collaboration with physicians from clinical departments of parent Institute and other local medical institutions.

Research interest. Research activity at the Center is devoted to translational research in experimental oncology and mainly pertains to molecular diagnostics and experimental therapies of cancer. Specifically, research activities are focused on: (i) genetic risk factor in cancer predisposition, (ii) novel prognostic and predictive markers for cancer therapy; (iii) genomic and proteomic signatures for cancer identification and classification; (iv) novel diagnostic tools for monitoring therapy; (v) pharmacology and biology of novel anticancer drugs; (vi) novel vectors and strategies of drug delivery.

Collaboration. Ongoing collaborative projects with prestigious scientific centers in Europe, USA and Canada, including: Columbia University, New York (USA); Deutsches Krebsforschungszentrum, Heidelberg (Germany); IARC, Lyon (France); Turku University (Finland); the National Cancer Institute, NIH, Bethesda (USA); University of Texas Southwestern Medical Center, Dallas (USA); Thomas Jefferson University, Philadelphia (USA); the Karolinska Institutet, Stockholm, (Sweden); the Institute of Industrial Medicine, Milan (Italy); Laval University, Quebec (Canada), Rice University, Houston (USA).
Research groups cooperate actively with a team of mathematicians and computer scientists from the Silesian University of Technology in Gliwice, who specialize in biostatistics and mathematical analyses of biological phenomena. The Center's staff is involved in graduate programs offered by three Silesian institutions of higher education: the Silesian University (Faculties of Biology and Physics), the Silesian Medical University and the Silesian University of Technology.

Relevant web pages:
Annual conference – Gliwice Scientific Meetings: **http://gsn.io.gliwice.pl/**

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RESEARCH PROFILE

Molecular genetics and molecular epidemiology of cancer, mechanisms controlling stability of the genome, mechanisms of cellular senescence, molecular mechanisms of cancer cell migration, regulation and function of heat shock genes in carcinogenesis and differentiation, search for molecular and immunohistochemical tumor markers, study of novel anticancer drugs and therapies.

CURRENT RESEARCH ACTIVITIES

Identification of genetic markers of lung cancer. We search for genetic markers, which may be useful in determining the individual risk of cancer. Using DNA samples isolated from lung cancer patients and healthy controls, we genotype the polymorphisms of genes coding for cytoprotection proteins. With this case–control approach we analyze dozens of genetic markers (polymorphisms) using PCR-RFLP or DNA sequencing methods. We study genetic host factors that modulate response to therapy in lung cancer patients searching for polymorphisms that may serve as prognostic or predictive factors. Germline p53 mutation in lung or breast cancer patients with strong family history of cancer is also analyzed. [M.Rusin, rusinm@rocketmail.com; D. Butkiewicz, dorotab@rocketmail.com]

Molecular and functional characterization of genes and proteins involved in maintenance of genomic stability, regulation of cellular senescence and cell cycle checkpoints. Maintenance of genomic stability protects against cancer and delays the appearance of aging. The cellular senescence that is a significant anticancer mechanism contributes to many signs of aging. The maintenance of genomic stability and cell cycle regulation are tightly coordinated. We study many aspects of this regulation. The group of genes and proteins studied by us include: RecQ helicases (WRN, BLM, RTS) associated with human cancer prone syndromes, SIRT1 deacetylase that regulates lifespan of model organisms, *BRCA1*, which is a major tumor suppressor gene, PML protein positively regulating many anticancer responses as well as other elements of cell cycle checkpoints. Project is held in cooperation with the Laboratory of Human Carcinogenesis, NCI, NIH, Bethesda, MD, USA. [M. Rusin, rusinm@rocketmail.com; D. Butkiewicz, dorotab@rocketmail.com]

Molecular profile of hereditary and sporadic breast cancer. About 10% of breast cancer cases develop on the background of hereditary predisposition. Among known predisposing mutations are those in BRCA1, BRCA2, p53, ATM genes and probably also mutations in CHEK2, NOD1, NBS1 genes. Large number of familial breast cancer cases have unknown genetic background; those are called BRCAx cases. We compared gene expression profile of hereditary breast cancer (BRCA1 mutation-linked and BRCAx cases) and sporadic breast cancer. Interestingly, we found, that BRCAx tumors have more distinctive gene expression profile from sporadic tumors than BRCA1-linked onesWe also analyzed whether similar phenotypic effects may be caused by different molecular events: *BRCA1* gene mutations and epigenetic silencing due to promoter hypermethylation. We found no difference in gene expression profile between breast cancer samples from *BRCA1* mutation carriers and samples with proven *BRCA1* promoter methylation. This indicates that both manners of *BRCA1* gene inactivation give rise to a similar phenotype of breast cancer. Taking into account the results of our microarray analysis, we suggest that the majority of *BRCA1*-linked breast cancers have a molecular profile of basal-like cancer. Thus, clinical observations and therapeutic recommendations that are true for basal-like breast cancer may as well apply to the hereditary *BRCA1*-mutated cancer. However, the question that still remains open, is why *BRCA1*-mutated tumors develop mostly as basal-like subtype. We also conclude that in the molecular studies on hereditary breast cancer *BRCA1* promoter methylation should be recognized and considered together with gene mutation.
Currently we validate usefulness of several selected genes/proteins as molecular markers of BRCA1 mutation-linked breast cancer. When positively validated such markers would be used to pre-screen breast cancer patients for possible BRCA1 mutation in cases with non-informative familial history of cancer. [K. Lisowska, kasial@io.gliwice.pl]

Molecular profile of ovarian cancer. Early stage ovarian cancer is characterized by asymptomatic development. Due to the lack of reliable biochemical tests and other diagnostic procedures suitable for screening and early detection, ovarian cancer is usually diagnosed at an advanced stage. Standard therapy for advanced stage ovarian cancer encompasses surgery aimed to maximal possible cytoreduction and adjuvant chemotherapy. Modern chemotherapeutic regimens are based on platinum compounds and taxanes. Ovarian cancer usually responds well to these therapies, however the development of drug resistance in many cases is the major obstacle limiting success rate. In a long run the aim of our study is to determine gene expression profile (gene signature) which is correlated with chemoresistance against different types of chemotherapy. We look for genes/proteins that could be used for prediction of individual patient response to the therapy. For better understanding the biology of ovarian cancer we are analyzing the main sources of variability and their impact on gene expression profiles in ovarian cancer. We also investigate the correlation between hereditary mutations in BRCA1 gene as well as somatic mutations in p53 gene and changes in global gene expression profile. Data analysis has shown that ovarian cancer samples from woman with hereditary *BRCA1* mutation have different gene expression profile than samples from woman without such mutation. With uncorrected p<0,001, 385 genes with differential expression were selected while with the criterion of false discovery rate (FDR) less than 10% these were 150 genes. Analyses of biological significance of selected genes showed that many of them are engaged in the regulation of cell cycle, apoptosis and DNA repair (Biocarta algorythm, www.Biocarta.com). Analysis of gene ontology (www.geneontology.org) indicated involvment of genes engaged in metabolic processes such as glycolysis, lipid synthesis, terpene metabolism and cellular respiration.
Classification of tumors from woman with and without *BRCA1* mutation on the basis of expression profile of selected genes yielded 79% accuracy (70% sensitivity, 79% specificity). For critical assessment of other features affecting the results of analysis concerning *BRCA1* mutation, other traits were also analyzed in univariate as well as multivariate analyses. These showed that *BRCA1* mutation is not the strongest feature affecting global gene expression profile, however it is significant also in multivariate comparison along with *TP53* mutation, tumor histology and residual tumor size.
Project is held in cooperation with the Department of Pathology, Cancer Center and Institute of Oncology, Warszawa. [K. Lisowska, kasial@io.gliwice.pl]

Application of laser-assisted microdissection for gene expression profiling in thyroid cancer. The project of gene expression profiling in papillary thyroid cancer is held in cooperation with Nuclear Medicine and Endocrine Oncology Department. Pure cell populations (thyreocytes, stromal cells, endothelial cells and inflammatory cells) are isolated with laser microdissection technique. Compared to RNA from bulk material now even slight differences in gene expression become detectable by quantitative RT-PCR or DNA microarrays. [A. Rusin, arusin@io.gliwice.pl]

The function of HSP70 genes (mainly human HSP70i and HSPA2 genes) in cancer cells. Stress-inducible protein HSP70i is frequently constitutively expressed at high levels in primary tumors. Moreover, we found that tumor cells as well as primary tumor tissue can express the *HSPA2* gene primarily defined as testis-specific *Hsp70*-related gene. Our main interest is to determine the functional differences (mainly cytoprotective and antiapoptotic role) between inducible Hsp70 and HspA2 proteins in cancer cells. We are also studying the influence of these proteins on different cell death pathways. We are working with *in vitro* cellular models based on overxpression or downregulation of *HSP70* genes. Using the

immunohistochemical methods we study the expression pattern of these proteins in human normal and neoplastic tissues. [D. Ścieglińska; dorotas@io.gliwice.pl]

Novel genistein derivatives as anticancer cytostatic drugs and radiosensitizers. Flavonoids are known to enhance radiosensitivity due to inhibition of the cell cycle progression in the phase G2/M. New genistein derivatives, patented by Pharmaceutical Institute are highly effective G2/M blockers, and show ability to disrupt mitotic spindles. The aim of a study is to test radiosensitizing properties of new genistein derivatives in prostate cancer cell lines. Project is held in cooperation with the Pharmaceutical Institute, (Warsaw), Institute of Immunology and Experimental Therapy, polish Acadmy of Science (Wrocław); CoE BioExploratorium, University of Warsaw; Silesian Polytechnic School, Department of Chemistry (Gliwice).[A. Rusin, arusin@io.gliwice.pl; Z. Krawczyk, krawczyk@io.gliwice.pl]

Gene expression profile of melanoma cells under hypoxic conditions. Hypoxia is an important feature of tumor microenvironment, exerting far-reaching effects on cells and contributing to cancer progression. Our high-density oligonucleotide microarrays based analysis performed on of B16 (F10) murine melanoma cells led to identification of several classes of genes differentially regulated by hypoxia. Currently, we work on validation of the gene signature of hypoxia *in vivo* (mouse model), as well as in human melanoma cell lines. In the near future we will extend microarray analysis to the human tumor cell lines (ovarian, prostate and breast cancer) grown in hypoxia. [M. Olbryt, molbryt@io.gliwice.pl]

The molecular mechanisms of a cell type-specific function of Heat Shock Transcription Factor 1 (HSF1). HSF1 is activated under stress conditions. In the majority of somatic cells activation of HSF1 leads to synthesis of heat shock proteins, which is a part of cytoprotective response. Our results indicate that in differentiating male germ cells HSF1 induces receptor-mediated and mitochondria-mediated apoptosis that is not prevented by HSP70i. The main aim of our work is to identify genes that are differentially expressed in somatic *versus* spermatogenic cells upon activation of HSF1. [Wieslawa Widlak, wwidlak@io.gliwice.pl]

Selected Papers:

Nagy E, Balogi Z, Gombos I, Åkerfelt M, Björkbom A, Balogh G, Török Z, Maslyanko A, Fiszer-Kierzkowska A, Lisowska K, Slotte P J, Sistonen L, Horváth I, Vigh L (2007): Hyperfluidization-coupled membrane microdomain reorganization is linked to activation of the heat shock response in a murine melanoma cell line. ***Proc Natl Acad Sci USA*** 104: 7945-7950

Pigłowski W, Nowak R, Krawczyk Z, Ścieglińska D (2007): The structural and functional analysis of the human HSPA2 gene promoter region. ***Acta Biochim. Polon.*** 54: 99-106

Popanda O, Edler L, Waas P, T. Schattenberg, D. Butkiewicz, T. Muley, H. Dienemann, A. Risch, H. Bartsch, P. Schmezer (2007): Elevated risk of squamous-cell carcinoma of the lung in heavy smokers carrying the variant alleles of the TP53 Arg72Pro and p21 Ser31Arg polymorphisms. ***Lung Cancer*** 55: 25-34

Vaitiekunaite R, Butkiewicz D, Krześniak M, Przybyłek M, Gryc A, Śnietura M, Benedyk M, Harris CC, Rusin M (2007): Expression and localization of Werner syndrome protein is modulated by SIRT1 and PML. ***Mech. Ageing Dev.*** 128: 650-651

Widłak W, Vydra N, Dudaladava V, Ścieglińska D, Winiarski B, Krawczyk Z (2007): The GC-box is critical for high level expression of the testis-specific Hsp70.2/Hst70 gene. ***Acta Biochim. Polon.*** 54: 107-112

Widłak W, Vydra N, Małusecka E, Dudaladava D, Winiarski B, Ścieglińska D, Widłak P (2007): Heat shock transcription factor 1 down-regulates spermatocyte-specific 70 kDa heat shock protein expression prior to the induction of apoptosis in mouse testes. ***Genes Cells*** 12: 487-499

Widłak W, Winiarski B, Krawczyk A, Vydra N, Małusecka E (2007): Inducible 70 kDa heat shock protein does not protect spermatogenic cells from damage induced by cryptorchidism. ***Int. J. Androl***. 30: 80-87

Butkiewicz D, Rusin M, Harasim J, Gawrychowski J, Czyżewski K, Chorąży M (2008): Single nucleotide polymorphisms in DNA repair genes predict overall survival in non-small cell lung-cancer patients. ***Radiother. Oncol.*** 88 (Suppl 2): S456

Gogler A, Rusin A, Grynkiewicz G, Krawczyk Z (2008): Antimitotic activity of novel sythetic genistein derivative. ***Acta Biochim. Polon.*** 55 (Suppl. 3): 289

Juzwa M, Rusin M, Zawidlak-Węgrzyńska B, Krawczyk Z, Obara I, Jedliński Z (2008): Oligo(3-hydroxybutanoate) conjugates with acetylsalicylic acid and their antitumour activity. ***Eur. J. Med. Chem***. 43: 1785-1790

Krześniak M, Butkiewicz D, Rusin M (2008): The functional impact of sequence alterations in WRN and RECQL helicase genes on the activity and intracellular localization of the proteins. ***Acta Biochim. Polon.*** 55 (Suppl. 3): 290

Kus-Liśkiewicz M, Jarząb M, Olbryt M, Widłak W (2008): Mechanism of apoptosis induced by heat shock transcription factor HSF-1; analyses of global gene expression profiles in cells differing in thermotolerance. ***Acta Biochim. Polon.*** 55 (Suppl. 3): 41

Lisowska K, Jarząb M, Olbryt M, Dudaladava V, Pamuła J, Simek K, Grzybowska E, Kupryjańczyk J (2008): Genomics studies on breast and ovarian cancer. *Acta Biochim. Polon.* 55 (Suppl. 3): 284

Małusecka E, Krzyżowska-Gruca K, Gawrychowski M, Fiszer-Kierzkowska J, Kołosza Z, Krawczyk Z, (2008): Stress proteins HSP27 and HSP70i predict survival in non-small cell lung carcinoma. ***Anticancer Res.*** 28: 501-506

Olbryt M, Tyszkiewicz T, Rusin A, Cichoń T, Lisowska K, Krawczyk Z (2008): Gene expression signature of hypoxia in murine melanoma cells B16(F10). ***Acta Biochim. Polon.*** 55 (Suppl. 3): 294

Ścieglińska D, Pigłowski W, Mazurek A, Małusecka E, Żebracka J, Filipczak P, Krawczyk Z (2008): The HspA2 protein localizes in nucleoli and centrosomes of heat shocked cancer cells. ***J. Cell Biochem***. 104: 2193-2206

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RESEARCH PROFILE

Research currently pursued at this Department is concerned with designing novel and specific strategies of destroying neoplastic tumors. Investigations have been focusing in particular on the application of antivascular proteins and peptides in combination with chemo-and radiotherapy.

The following research topics have been of particular interest to this group:

1. Two-domain antivascular proteins. Peptides in tumor therapy. Novel drug carriers.

2. Novel antitumor strategies: the tumor microenvironment as a target.

3. Epidemiology of breast cancer; hereditary predisposition to breast and ovarian cancers; identification of new genes modifying predisposition to breast cancer.

CURRENT RESEARCH ACTIVITIES

Cancer Genetics Laboratory

Molecular mechanisms in endometrioid and clear-cell ovarian cancer development. The Project goal is to investigate molecular mechanisms linked to progression in clear-cell ovarian cancer and comparison of its gene expression profile with that of serous and endometrioid ovarian cancers.

Frequency of heterozygotic mutations in NBS1 gene in familial cancers. The goal of this Project is to establish occurrence of mutation frequency in exon 6 of NBS1 gene within families with aggregate cancers, especially melanoma as well as breast and ovary cancers.

Assessment of frequency of germline mutation carriers in BRCA1 and CHEK2 genes in Polish population - including regional variation and cancer morbidity structure in gene carriers families. The aim of this Project is to assess mutation frequency in BRCA1, CHEK2 and NBS1 genes based on samples from anonymous Silesia district donors.

Molecular and genetic epidemiology of cancers on the basis of cancer registers and tissue banks. The Cancer Genetics lab group forms part of a research project team involving 21 members from nine European Union countries. The research goals of this group, which studies genetic epidemiology of various cancers, include identification of new neoplasia-linked genes, determining familial predisposition risk for the prevailing cancer localizations, assessing ratios of neoplasms linked to specific gene mutations as well as estimating population frequency of these genes and their penetrance.

Genetic diagnostics for breast and ovary cancer predisposition. In collaboration with the **Molecular Diagnostics and Cancer Genetic Counseling** genetic counseling is provided and genetic tests performed in patients with familial predisposition for breast and ovarian cancers. Hereditary predisposition to these cancers is tested in both afflicted and healthy individuals.

Main research techniques: Research projects and genetic diagnostics are based on DNA tests employing PCR (ASA-PCR, RFLP-PCR) and sequencing techniques.

Experimental Cancer Therapy Laboratory

ABRaA-$VEGF_{121}$, a two-domain protein in anticancer therapy. The goal of this Project is to construct a two-domain fusion protein. One of its domains, exerting the therapeutic effect, is formed by A chain of abrin (ABRaA), a plant toxin. The other domain, responsible for recognition of target cells is made up by $VEGF_{121}$ isoform. The fusion protein is isolated and purified from suitable E.coli strains.

Peptides in anticancer therapy. The aim of the Project is the construction and therapeutic use of peptides recognizing and destroying both neoplastic cells and cells forming tumor microenvironment.

Induction of immune response against of tumor vessel endothelial cells via administration of oral DNA vaccines. The goal of this Project is to use modified *Salmonella typhimurium* bacteria as a carrier of endoglin gene. Endoglin induces specific immune response against tumor vessel endothelial cells.

Targeted shielded nanocarriers in the transfer of anticancer drugs. Construction of nanocarriers (liposomal and polymeric) capable of transporting anticancer drugs. Novel therapeutic combinations involving antivascular oligopeptides allowing selective recognition and destruction of tumor endothelium and chemotherapeutics delivered by PEG-coated liposomes.

Main research techniques: Gene construction and cloning. In vitro and in vivo gene transfer.

Bacterial and eukaryotic cell culture. Expression, isolation and purification of recombinant proteins. Chemical synthesis. Preparation of liposomes and other nanocarriers. Experimental therapy of tumor-bearing mice. Apoptosis tests (TUNEL and determination of caspase 3). Assessment of neovascularization degree in primary tumors. Immunohistochemistry.

Selected Papers:

Forsti A, Jin Q, Altieri A, Johansson R, Wagner K, Enqist K, Grzybowska E, Pamuła J, Pękala W, Hallmans G, Lenner P, Hemminki K (2007): Polymorphism in the KDR and POSTN genes: association with breast cancer susceptibility and prognosis. ***Breast Cancer Res. Treat.*** 101: 83-93

Gabrys D, Behrendt K, Grzybowska E, Suwinski R, Idasiak A, Galwas K, Boratyn A, Wojcieszek P, Pekala W, Pamula-Pilat J, Budryk M, Nowicka E, Thames H.(2007): Characteristics and outcome of young breast cancer patients with and without BRCA1 mutations. ***Eur J Cancer*** 2007 **93**: 513

Jazowiecka-Rakus J, Jarosz M, Kozłowska D, Sochanik A, Szala S (2007): Combination of vasostatin and cyclophosphamide in the therapy of murine melanoma tumors. ***Acta Biochim. Polon.*** 54: 125-133

Wagner K, Grzybowska E, Butkiewicz D, Pamula-Pilat J, Pekala W, Tecza K, Hemminki K, Forsti A (2007): High-throughput genotyping of a common deletion polymorphism disrupting the TRY6 gene and its association with breast cancer risk. ***BMC Genet.*** 8: 41: 1-10

Byrski T, Gronwald J, Huzarski T, Grzybowska E, Budryk M, Stawicka M, Mierzwa T, Szwiec M, Wiśniowski R, Siołek M, Narod SA, Lubiński J (2008). Response to neo-adjuvant chemotherapy in women with Brca1-positive breast cancers. ***Breast Cancer Res. Treat.*** 108: 289-296

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Hutka M, Tarnawski R, Budryk M, Pamuła-Piłat J, Tęcza K, Grzybowska E, Wysocki P (2008): Clinicopathologic characteristics of epithelial ovarian cancer in patiens with BRCA1 and BRCA2 mutation in Polish population - observational study. ***Ecancermedicalscience***.

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Jakub Hanus, M.Sc.

Robert Herok, M.Sc.

Karol Jelonek, M.Sc.

Katarzyna Szołtysek, M.Sc.

Anna Walaszczyk, M.Sc.

RESEARCH PROFILE

The research interest of the Department is focused on molecular mechanisms of cellular response to ionizing radiation and other genotoxic factors, individual radio-sensitivity in human population, proteomic signatures for cancer identification and classification, molecular factors involned in apoptosis and DNA repair.

CURRENT RESEARCH ACTIVITIES

- DNA damage and repair, studied on normal and tumor cells; genetic factor involved in responses to genotoxic damage and DNA repair; the individual variability of radiosensitivity of cancer patients and healthy subjects [J.Rzeszowska, jrzeszowskawolny@yahoo.com]

- The identification of genes, proteins and pathways that are involved in cellular responses to radiation and modulate the radiation sensitivity of normal and malignant cells; functional genomics and bioinformatics in radiobiology [J.Rzeszowska, jrzeszowskawolny@yahoo.com]

- Factors that modify cellular responses to ionizing radiation; the influence of antioxidants on DNA damage induced by radiation; the effects of scattered radiation [J.Rzeszowska, jrzeszowskawolny@yahoo.com; M. Konopacka, m_konopacka@epf.pl]

- The bystander effect and its role in cellular responses to ionizing radiation [J.Rzeszowska, jrzeszowskawolny@yahoo.com; M. Wideł, widel@io.gliwice.pl]

- Proteomic signatures for cancer identification and classification; mass spectrometry-based analyses of blood proteome patterns [P. Widłak, widlak@io.gliwice.pl, M.Pietrowska, m_pietrowska@io.gliwice.pl]

- The regulation of molecular processes involved in terminal stages of apoptosis: DNA fragmentation and chromatin condensation; mechanism of regulation and function of major apoptotic nuclease DFF40/CAD [P. Widłak, widlak@io.gliwice.pl]

- Modelling of regulatory circuits of signaling pathways involved in cancer cell biology; functional interactions of pathaways depending on NFkB, p53 and HSF1 transcription factors [P. Widłak, widlak@io.gliwice.pl; M. Kalinowska-Herok, mkalinowska@io.gliwice.pl]

- The mechanism of radiation-induced damage to non-target tissues; the mechanism of cardiovascular risk after low radiation doses – SP5 Euratom Collaborative Project CARDIORISK [P. Widłak, widlak@io.gliwice.pl]

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Prof. **Ronald Hancock**, Ph.D., Laval University, Quebec, Canada

Prof. **Marek Kimmel**, Ph.D., Rice University, Houston, USA

Prof. **Ryszard Olinski**, Ph.D., Nicolaus Copernicus University, Bydgoszcz, Poland

Prof. **Andrzej Polański**, Ph.D., Silesian University of Technology, Gliwice, Poland

Prof. **Joanna Polańska**, Ph.D., Silesian University of Technology, Gliwice, Poland

Prof. **Maciej Stobiecki,** Ph.D., Institute of Organic Chemistry, Poznań, Poland

Prof. **Barbara Tudek**, Ph.D., Institute of Biochemistry and Biophysics, Warszawa, Poland

Selected Papers:

Horak S, Olejek A, Widłak P (2007): Sperm DNA adducts impair fertilization during ICSI but not during IVF. ***Folia Histochem. Cytobiol.*** 45: 1-6

Xiao F, Widłak P, Garrard WT (2007): Engineered apoptotic nucleases for chromatin research. ***Nucl. Acids Res.*** 35, e93

Chwieduk A, Slonchak A, Ścieglińska D, Rzeszowska-Wolny J (2008): Expression of glutathione S-transferase P1-1(GSTP1) In cultured human cells and chan ges induced by ionizing radiation. ***Acta Biochim Polon.*** 55 (Suppl.3): 299

Hanus J, Kalinowska-Herok M, Widłak P (2008): The major apoptotic endonuclease DFF40/CAD is a deoxyribose-specific and double-strand-specific enzyme. ***Apoptosis*** 13: 377-382

Jaksik R, Polańska J, Rzeszowska-Wolny J (2008): The 3' non-coding nucleotide sequence influences RNA stability in irradiated cells. ***Acta Biochim Polon.*** 55 (Suppl.3): 316

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Laboratory of Molecular Diagnostics and Functional Genomics

within

Department of Nuclear Medicine and Endocrine Oncology

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RESEARCH PROFILE

The research projects are focused on studies of genetic predisposition to neoplasms of endocrine glands and other hereditary neoplasms, functional genomics of endocrine cancer, molecular cancer markers and their clinical applications, molecular radiobiology of thyroid cancer, targeted therapy of endocrine cancer. We perform translational research, both in molecular diagnostics and molecular therapy of thyroid cancer, other endocrine-related cancers and adenomas. We analyze hereditary/somatic mutations and single nucleotide polymorphisms, changes in gene expression at single gene and genomic level, apply bioinformatic methods to study cancer transcriptome, to derive novel clinically relevant molecular markers and to analyze the biology of endocrine-related cancer. The laboratory carries out own research and provides molecular services as core laboratory (oligonucleotide microarray analysis, real time Q-PCR , sequencing)

Specific topics include: gene expression profiling in tumors (thyroid, parathyroid, adrenals, pituitary, breast, lung, pancreas, head and neck); genetic predisposition to medullary thyroid carcinoma and pheochromocytoma, genetic presisposition to differentiated thyroid cancer; somatic mutations and chromosomal rearrangements in papillary and medullary thyroid carcinomas; the role of thyroglobulin as an early marker of differentiated thyroid carcinoma; novel targeted therapies in the treatment of differentiated and medullary thyroid cancer.

Clinical research of the Department is focused on application of molecular techniques into clinical practice of endocrine oncology and development of new diagnostic and therapeutic methods. In medullary thyroid cancer patients new targeted therapy is under evaluation. There is an ongoing project on clinical application of radiolabelled somatostatin analogues in treatment of endocrine malignancies. In differentiated thyroid cancer study on rh-TSH in treatment of disseminated disease is continued and evaluation of long-term side effects of radionuclide therapy was initiated.

Cooperation with other centers. The Laboratory acts on two levels:

1. "Core laboratory" which includes 3 units providing molecular services: microarray laboratory, QPCR laboratory and sequencing laboratory.
2. Cooperation with:
   - Professor Mike Atkinson, GSF -National Research Center for Environment and Health, Germany and Dr. Gerry Thomas, South West Wales Cancer Institute, Swansea, Walia (common project FP6/STREPS: Genetic component of the low dose risk of thyroid cancer);
   - Professor Ralf Paschke, University of Leipzig, Germany (common study on transcriptome of thyroid nodules, application of new molecular markers of follicular carcinoma);
   - Professor Martin Schlumberger, Institute Gustave-Roussy, France (targeted therapy trials)
   - Professor Massimo Santoro, Dipartimento di Biologia e Patologia Cellulare e Molecolare, Neapol (functional genomic of thyroid cancer)
   - Professor Christopher Reiners, Klinik und Poliklinik für Nuklearmedizin Universitätsklinikum Würzburg (radioiodine therapy, childhood thyroid carcinoma)
   - Professor Richard Baum, Zentralklinik Bad Berka, Germany (targeted therapy of neuroendocrine tumors)
   - Professor Andrzej Januszewicz, Institute of Cardiology, Warsaw (genetic predisposition to pheochromocytoma)
   - Professor Jacek Jassem, Medical University of Gdańsk (gene expression profile of lung cancer)
   - Professor Paweł Lange and Dr. Marek Olakowski (gene expression profile of pancreatic cancer)
   - Dr. Tomasz Bednarczuk, Department of Endocrinology, M. Mossakowski Medical Research Center, Polish Academy of Sciences, Warsaw and Dr Y. Hiromatsu, Department of Endocrinology and Metabolism, Kurume University School of Medicine, Fukuoka, Japan (multigene predisposition to Graves-Basedow disease)
   - Dr. Tatiana Gierek and Dr. Jarosław Markowski, Clinic of Laryngology, Silesian Medical University, Katowice (gene expression profile of larynx cancer)
   - Professor Tomasz Kręcicki, Clinic of Otolaryngology, Medical Academy of Wroclaw (molecular profile of head and neck carcinomas)

   The major projects performed in cooperation:
   - ❖ Sixth Research and Technological Development Framework Programme of the European Commision "Generisk-T"
   - ❖ Research project nr PBZ-MNiI-2/1/2005. The analysis of interferences in cell transduction pathways in cancer pathogenesis with the application of methods of integrating genomics.
   - ❖ Research project nr 2PO 5B 085 26. The frequency of incidence of SDHB, SDHD and other gene mutations in patients with pheochromocytoma based on national register.

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Bausch B, Borozdin W, Mautner VF, Hoffmann MM, Boehm D, Robledo M, Cascon A, Harenberg T, Schiavi F, Pawlu C, Peczkowska M, Letizia C, Calvieri S, Arnaldi G, Klingenberg-Noftz RD, Reisch N, Fassina A, Brunaud L, Walter MA, Mannelli M, Macgregor G, Palazzo FF, Barontini M, Walz MK, Kremens B, Brabant G, Pfaffle R, Koschker AC, Lohoefner F, Mohaupt M, Gimm O, Jarząb B, McWhinney SR, Opocher G, Januszewicz A, Kohlhase J, Eng C, Neumann HP (2007): Germline NF1 Mutational Spectra and Loss-of-Heterozygosity Analyses in Patients with Pheochromocytoma and Neurofibromatosis Type 1. ***J Clin Endocrinol Metab***. 92: 2784-2792

Eszlinger M, Krohn K, Kukulska A, Jarząb B, Paschke R (2007): Perspectives and limitations of microarray-based gene expression profiling of thyroid tumors. ***Endocr Rev***. 28: 322-338

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Polański A, Polańska J, Jarząb M, Wiench M, Jarząb B (2007): Application of Bayesian networks for inferring cause-effect relations from gene expression profiles of cancer versus normal cells. ***Math Biosci***. 209: 528-46

Jażdżewski K, Murray EL, Franssila K, Jarzab B, Schoenberg DR, de la Chapelle A.(2008); Common SNP in pre-miR-146a decreases mature miR expression and predisposes to papillary thyroid carcinoma. ***Proc. Natl. Acad. Sci. USA*** 105: 7269-7274

Jarząb B, Wygoda Z, Pawalczek A, Gubała E, Szpak-Ulczok S, Hasse-Lazar K, Krawczyk A, Chmielik E, Lange D, Pęczkowska M, Prejbisz A, Januszewicz A (2008): Comparison of germline RET mutations between carriers recruited by the presence of medullary thyroid cancer or by pheochromocytoma/paraganglioma. ***Hormones*** 7: 47

Jarzab M, Różanowski P, Kowalska M, Zebracka J, Rudnicka L, Stobiecka E, Jarzab B, Stachura J, Pawlega J (2008): Optimization of the method of RNA isolation from paraffin blocks to assess gene expression in breast cancer**. *Pol. J. Pathol.*** 59: 85-91

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Laboratory of Molecular Radiobiology

within

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RESEARCH PROFILE

The Laboratory of Molecular Radiobiology, organized in 2008, focuses on application of molecular markers in clinical practice, mainly in radiotherapy. Molecular markers enables to assign patient to therapy responders vs nonresponder group, gives the information on individual predisposition and treatment outcome, making individual "tailoring" therapy achievable.

CURRENT RESEARCH ACTIVITIES

Identification and validation of radiotherapy predictive markers. Achievements of modern radiotherapy facilitate precise delivery of radiation dose diminishing risk of side effects. Therefore identification of genes involved in radiation response is of great interest. We studied the expression of "radiation classifier" genes (RGS19, RbAp48, R5PIA) by means of quantitative, reverse PCR and proteins coded by these genes (by immunohistochemistry). Results of the assay were compared to bax/bcl2 staining, described earlier as radiotherapy outcome marker. [Ewa Małusecka, maluseck@io.gliwice.pl]

Involvement of stromal cells in cancer incidence and progression. The study is focused on identification of specific proteins in cancerous stroma, which may be used for improvements in diagnosis and prediction of recurrence. We work on the model of human prostate. Stromal cells of normal prostate and prostate cancer are isolated by laser-captured microdissection. After RNA isolation the expression analysis is performed using microarray analysis and quantitative, reverse PCR. [Anna Fiszer-Kierzkowska, anna.fiszer@plusnet.pl]

Mismatch Repair Genes (MLH1, MSH2, MSH6, PMS2) analysis as a diagnostic tool in Lynch Syndrome. Expression of genes involved in DNA repair (MMR) is applied in molecular diagnosis of hereditary non-polyposis colon cancer (HNPCC) and other types of hereditary-related cancers. [Agnieszka Mazurek, agmaz@yahoo.com]

Fiszer-Kierzkowska A, Malusecka E, Jarząb M, Gawkowska-Suwinska M, Rembak-Szynkiewicz J, Bobek-Billewicz B, Jarząb B, Maciejewski B (2008): Molecular changes in histopatologically normal prostate tissue adjacent to cancer. ***Eur J Cancer Suppl***. 6: 109-110

Małusecka E, Fiszer-Kierzkowska A, Jarząb M, Kowalska M, Gawkowska-Suwińska M, Wolańska K, Zborek A, Rembak-Szynkiewicz J, Bobek-Bilewicz B, Zajusz A, Krawczyk Z, Maciejewski B (2008): Potential predictive value of „radiosensitivity classifier" in prostate cancer. ***Radiother Oncol*** 88 (Suppl 2): S 474

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Laboratory of Biophysics

Head: **Maria Sokół**, Ph.D. (mary@io.gliwice.pl)

The laboratory brings together physicists, biologists and chemists engaged in the studies of brain biochemistry using NMR spectroscopy. Research is focused on the studies of intact biological systems by MRS in vivo and the high resolution in vitro NMR model studies of animal brain extracts and cell lines.
The main scientific interests involve:

- Application of ^{1}H MR in vivo spectroscopy and multivariate statistical methods (PCA, PLS-DA, OSC) in the studies of brain glial tumor metabolic profiles and uncertain zone analyses.
- Detection of early and late metabolic effects of brain irradiation using ^{1}H MRS *in vivo*, ^{1}H NMR *in vitro* of C6 cell line and multivariate statistical methods (PCA, PLS-DA, OSC).
- Investigation of brain metabolism disturbances in smokers and in patients with lung cancers – multivariate statistical analyses (PCA, PLS-DA, OSC) of NMR data and comparative animal model studies.
- Evaluation of usefulness of ^{1}H MRS *in vivo* in diagnostics of progressive encephalopathies in children.

Laboratory of Dosimetry and Quality Control in Radiotherapy and Rentgenodiagnostics

Head: Andrzej Orlef, Ph.D. (aorlef@io.gliwice.pl)

The focus of the research in this laboratory is the clinical implementation of improved treatment and verification methods, like portal imaging and in vivo dosimetry.
The new area of studies is 3D polymer gel dosimetry using MRI readout methods.

Selected Papers:

Matulewicz Ł, Sokół M, Polnik A, Wydmański J (2007): Multivariate analysis of ^{1}H NMR spectra as a tool to extract information on irradiation response of white matter. ***Radiother Oncol* 84**: 218-219

Boguszewicz Ł, Blamek S, Sokół M (2008): Pattern recognition methods in 1H in vivo MRS investigation of normal-appearing cerebellar tissue after cerebellum tumors treatment ***Radiother. Oncol.*** 88 (suppl 2): S427

Grobelny Z, Stolarzewicz A, Szczepański A, Sokół M (2008): Formation and decomposition of potassium potassides complexed crown ethers in tetrahydrofuran solution. ***Curr. Org. Chem.*** 12: 1040-1049

Konefał A, Orlef A, Maniakowski Z, Polaczek-Grelik K, Zipper W (2008): Correlation between radioactivity induced inside the treatment room and the undesirable thermal/ resonance neutron radiation produced by linac, ***Physica Med.*** 24: 212-218

Sokół M, Boguszewicz Ł, Jamróz E, Paprocka J, Wicher M, Polnik A (2008): Magnetic resonance spectroscopy and pattern recognition in central system disorders. ***J. Nucl. Med.*** 49 (Suppl. 1): 713

Department of Cancer Epidemiology

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RESEARCH PROFILE

The Department covers the following activities:

Cancer epidemiology studies. The analytical and descriptive studies are focused on:

- The rate analysis for the most frequent cancer sites (lung, breast and genitourinary organs) observed in Silesia District, classified by gender, age and period of calendar time.
- The oncocartography studying variations in cancer occurrence between different areas of Silesia District (on municipality level) or over time.
- An identification of important risk factors for selected cancer sites including lung, cervix and corpus uteri, breast, skin and larynx cancers.

The Regional Silesia Cancer Registry (RSCR)

RSCR is one of the 16 population-based cancer registries in Poland, covering a residential population of 4,9 million people living in highly polluted industrial Silesia District. RSCR routinely monitors cancer occurrence and aims to improve the quality and availability of the data. Together with data on death cases, the information collected by the registry is used to produce statistics about cancer incidence and mortality. It is a unique data resource for current and future research in cancer epidemiology. RSCR is fully computerized and routinely contributes the data to the National Cancer Registry. The registry is active in the collaboration with the Polish Association of Cancer Registries. In future, the work of cancer registry will expand from monitoring of cancer occurrence to the analysis of different aspects of cancer prevention, treatment and care.

Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch

The Comprehensive Cancer Center

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II[nd] Clinic of Radiotherapy

head: Dr. **Aleksander Zajusz**, M.D., Ph.D.

III[rd] Clinic of Radiotherapy

head: Dr. **Sylwia Jędruś**, M.D., Ph.D.

Clinic of Oncological and Reconstructive Surgery

head: Dr. **Stanisław Półtorak**, M.D., Ph.D.

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head: Professor **Bogusław Maciejewski**, M.D., Ph.D.

Department of Tumor Pathology

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Outpatient Clinic

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Selected papers published in years 2007-2008:

Bujko K, Michalski W, Kepka L, Nowacki MP, Nasierowska-Guttmejer A, Tokar P, Dymecki D, Pawlak M, Lesniak T, Richter P, Wojnar A, Chmielik E (2007): Polish Colorectal Study Group (2007): Association between pathologic response in metastatic lymph nodes after preoperative chemoradiotherapy and risk of distant metastases in rectal cancer: An analysis of outcomes in a randomized trial. *Int J Radiat Oncol Biol Phys*. **67**: 369-377

Gabryś D, Greco O, Patel G, Prise KM, Tozer GM, Kanthou C (2007): Radiation effects on the cytoskeleton of endothelial cells and endothelial monolayer permeability. *Int J Radiat Oncol Biol Phys*. **67**:1553-1562

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