## Contents

Molecular & Cellular Biophysics & Biochemistry Program .................................................. 2
About Buffalo, New York ........................................................................................................ 3
Map – Directions to Roswell Park Cancer Institute .............................................................. 3

## Faculty Research

### Robert E. Baier
Interfacial Biophysics, addressing structure and function of macromolecules at boundaries of living tissues with prosthetic devices such as artificial heart valves and dental implants

### Sathy V. Balu-Iyer (Sathyamangalam V. Balasubramanian)
Pharmaceutical Biotechnology; Formulation and Delivery of Protein Therapeutics

### David A. Bellnier
Photodynamic Therapy: Basic and Translational Research

### Mikhail V. Blagosklonny
Intracellular signal transduction pathways in cancer and aging

### William Cancé
Biology of focal adhesion kinase (FAK); Role of FAK in preventing apoptosis; Novel drugs that target FAK pathway; Other survival mechanisms of cancer cells

### Mikhail Chernov
Bioactive Small Molecules and Functional Screening

### Vita M. Golubovskaya
Focal Adhesion Kinase Expression and Signaling in cancer

### Andrei V. Gudkov
Cancer treatment and normal tissue protection by targeting major stress response pathways; functional screening approaches to gene and drug discovery.

### Katerina V. Gurova
Anti-cancer drug discovery through modulation of transcriptional factors activity in tumor cells

### Eugene S. Kandel
Genetic dissection of signal transduction in mammalian cells

### A. Latif Kazim
Biomolecular Resources: Proteomics, Mass Spectrometry, DNA Sequencing and NMR Spectroscopy; Research Interests: Proteomics, Metabolomics and Imaging Mass Spectrometry

### Eleva V. Kurenova
Protein complexes of Focal Adhesion Kinase as the targets in tumor growth, angiogenesis and metastasis

### Asoke K. Mal
Epigenetics, Transcription factors and Childhood Cancer

### Harish K. Malhotra
Applications of Medical Physics to cancer diagnosis and treatment

### Janet Morgan
Mechanisms and enhancement of Photodynamic Therapy in cancer and cancer stem cells

### Daryl P. Nazareth
Applications of Medical Physics to cancer diagnosis and treatment

### Mikhail A. Nikiforov
Molecular mechanisms of transformation and senescence

### Ravindra K. Pandey
Multifunctional agents for imaging and therapy

### Matthew B. Podgorsak
Applications of Medical Physics to Cancer Diagnosis and Treatment

### Arindam Sen
Nanoparticle drug formulation and tumor microenvironment

### Mukund Seshadri
Cancer Imaging/Targeted Therapies

### Joseph Spernyak
Magnetic resonance imaging in animal models of disease

### Robert M. Straubinger
Modulation of anticancer drug biodisposition and pharmacodynamics by drug carriers

### Ulas Sunar
Novel optical imaging techniques for therapy monitoring
Molecular & Cellular
Biophysics & Biochemistry

GRADUATE PROGRAM
“BETTER CANCER THERAPIES THROUGH KNOWLEDGE AND INNOVATION.”

The current understanding of cancer as a disease and clinical approaches to treating cancer have made enormous gains in the past couple of decades. This was made possible by tremendous technological advances that delivered unparalleled capabilities and a wealth of knowledge to the biomedical field. In our research, we use the insights into stress response mechanisms in normal and cancerous cells to improve the outcomes of cancer treatment, including the design of novel anti-cancer therapies, and amelioration of the side effects and enhancement of efficacy of the available ones.

Our faculty members maintain a strong tradition of technological innovation, which leads to the establishment of new concepts in treatment and diagnosis of the disease, and to the discovery of prospective therapeutic targets and potent chemotherapeutic agents. Our students are exposed to a challenging curriculum delivered by a team of experts from RPCI and other institutions and conduct high-impact research in several crucial and interlinked areas of modern oncology:

- Through the studies of signal transduction and gene regulation we expand the knowledge of the origins of cancer and the therapeutic responses of the disease.
- Gene and drug discovery capitalizes on our expertise in biology of normal and tumor cells in order to identify and characterize therapeutic targets and chemotherapeutic agents.
- Biophysical therapies intensively studied by our scientists include radiation, thermal and photodynamic (PDT) therapies. PDT has been developed at Roswell Park Cancer Institute and our Institution remains the world leader in research and clinical applications of this technology.
- Our teams of biophysicists, chemists, and molecular biology and nanotechnology experts develop and optimize cancer targeting strategies for drug delivery, as well as for imaging and diagnostic purposes.

Successful integration of basic and clinical research remains the main strength of Roswell Park Cancer Institute. A network of close collaborations with clinicians and industrial scientists expedites the transition of relevant findings “from bench to bedside” and provides a comprehensive and versatile training experience for our students.
About Buffalo, New York

Roswell Park Cancer Institute, one of the oldest cancer research institutes in the world, is located on several blocks near other hospitals within a mile of downtown Buffalo. Buffalo, the second largest city in New York, enjoys the cultural and social advantages of many larger cities and offers a relaxed pace of life and exceptionally easy access to the surrounding countryside and lakefronts. Located at the eastern end of Lake Erie, buffalo is 15 miles from Niagara Falls and across Lake Ontario from Toronto. Lake Erie moderates winter and summer temperatures and provides outstanding recreational opportunities in boating, swimming, fishing, and diving. The surrounding hills, fields, and forests in western New York and southern Ontario provide excellent downhill and cross-country skiing, hiking, and camping. Accessible, inexpensive, and convenient flights offer year-round access to New York and other major East Coast, Midwestern and Southern cities.

Directions to Roswell Park Cancer Institute
Interfacial Biophysics, addressing structure and function of macromolecules at boundaries of living tissues with prosthetic devices such as artificial heart valves and dental implants.

Robert E. Baier, PhD, PE
Professor and Director, Biomaterials Graduate Program
State University of New York at Buffalo

Beginning as a surgical technician operating heart-lung machine and dialysis equipment at the Buffalo General Hospital in 1959, he progressed through Bachelor of Engineering Science (Physics, Cleveland State University) and Ph.D. (Biophysics) degrees to post-doctoral training as a National Academy of Sciences fellow (Surface Chemistry) in Washington D.C. (1966-68). Dr. Baier spent sixteen years on the professional research staff of Calspan Advanced Technology Center prior to joining SUNYAB full time. He was Executive Director of the New York State Center for Advanced Technology in Health-care Instruments and Devices (1984-1989), and now is Executive Director of the Industry/University Center for Biosurfaces sponsored by the U.S. National Science Foundation. He is extensively published in many areas of biosurface physics, particularly involving dental and medical implant technology.

Dr. Baier is available for consulting assignments on a limited basis due to his teaching obligations in the Schools of Medicine, Dentistry, and Engineering.

EDUCATION/TRAINING

Cleveland State University (Cleveland, OH), B.E.S. 1962, Engineering Sci/Physics

State University of New York at Buffalo, Ph.D. 1966, Biophysics

National Academy of Sciences/National Research Council (Washington, DC), Postdoctoral Associate 1966-1968, Surface Chemistry [U.S. Naval Research Lab]
<table>
<thead>
<tr>
<th>Year</th>
<th>Position/Role</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988</td>
<td>Expert Panel, NIH Consensus Development Conference on “Dental Implants”</td>
<td>1987 Award for Innovation in Medical Devices, American Society for Artificial Internal Organs</td>
</tr>
<tr>
<td>1988-pres</td>
<td>Executive Director (Co-Director 1988-1992), NSF Industry/University Center for Biosurfaces, SUNY Buffalo</td>
<td>1989 Chairman, Gordon Research Conference on Biocompatibility and Biomaterials</td>
</tr>
<tr>
<td>1988-2004</td>
<td>Editorial Consulting Staff, The International Journal of Oral &amp; Maxillofacial Implants</td>
<td>1993 Founding Fellow, American Institute of Medical and Biomedical Engineering</td>
</tr>
<tr>
<td>1991-pres</td>
<td>Adjunct Professor, Center for Bioengineering &amp; Dept. Mechanical and Aerospace Eng., SUNY Buffalo</td>
<td>1994 Fellow, Biomaterials Science and Engineering, Int’l Union of Societies for Biomaterials Science &amp; Engineering</td>
</tr>
<tr>
<td>1992</td>
<td>Member, U.S. Army Research Laboratory (ARL) Biotechnology Assessment Committee</td>
<td>2000 Engineer of the Year Award, Fenn College of Engineering, Cleveland State University</td>
</tr>
<tr>
<td>1992-1993</td>
<td>President, Society For Biomaterials</td>
<td>2001 Humanitarian Award, Health Care Industries Association of the Niagara Frontier</td>
</tr>
<tr>
<td>2000</td>
<td>Expert Panel, NIH Technology Assessment Conference on Implant Retrieval</td>
<td></td>
</tr>
<tr>
<td>2000-pres</td>
<td>Editorial Board, The Journal of Adhesion</td>
<td></td>
</tr>
<tr>
<td>2004-pres</td>
<td>Member, U.S. Army Biotechnology Working Group</td>
<td></td>
</tr>
</tbody>
</table>

**Memberships:**

**Honors**
- 1971 Union Carbide Chemicals Prize, awarded by American Chemical Society
- 1983 Clemson Award for Basic Research, awarded by Society For Biomaterials, 1983

**Select Publications, including Relevant Abstracts and Proceedings (1995 - present)**


Professional Organizations
- Society for Biomaterials (Past President)
- American Institute for Medical and Biological Engineering (Vice President)
- Health Care Industries Association of the Niagara Frontier (Director)
- National Society of Professional Engineers
- American Chemical Society

Pharmaceutical Biotechnology; Formulation and Delivery of Protein Therapeutics

Dr. Sathy V. Balu-Iyer
(Sathyamangalam V. Balasubramanian)
Associate Professor, Pharmaceutical Sciences

Dr. Sathy V. Balu-Iyer (Sathyamangalam V. Balasubramanian) is an Associate Professor of Pharmaceutical Sciences. His research interest is in the area of Pharmaceutical Biotechnology, in particular, formulation and delivery of protein therapeutics using an interdisciplinary approach of Biophysics (Bioengineering), Immunology and Pharmacokinetics and Pharmacodynamics. Dr. Balu-Iyer is the Associate Director of the Pharmaceutical Sciences Instrumentation Facility. He was a post doctoral fellow in the Department of Pharmaceutical Sciences, State University of New York at Buffalo. He received his Ph.D. in Molecular Biophysics from the Indian Institute of Science in Bangalore, India.

Photodynamic Therapy: Basic and Translational Research

David A. Bellnier, PhD
Assistant Professor of Oncology

The objective of this program is to devise and implement more effective approaches to Photodynamic Therapy (PDT). PDT involves the administration of a photodynamically-active drug (photosensitizer) or pro-drug followed by drug-activating visible light. This therapy has been successfully applied to both neoplastic and non-neoplastic diseases.

This research program takes place in the multidisciplinary, highly interactive environments of the Photodynamic Therapy Center and the Biophysical Therapies Program. As such, numerous lines of attack are being taken to improve both the efficacy and selectivity of PDT, including (i) the rational design, synthesis and testing of new photosensitizers 1, 2 [directed by Dr. Pandey in our group], (ii) the design and application of optimal therapeutic regimens, e.g., drug dosage and schedule based on pharmacokinetic/pharmacodynamic studies3 [directed by Dr. Bellnier] and light dosage and schedule based on fluence/fluence rate studies4 [directed by Dr. Henderson in our group] and (iii) the study of multimodal approaches 5-7.
We have had a long-standing program to study the interaction between vascular disrupting agents (VDAs) and PDT. Much of our past and current work has focused on the antivascular agent vadimezan (DMXAA; 5,6-dimethylxanthenone-4-acetic acid) 4. Although vadimezan does not appear to be directly cytotoxic to tumor cells, it induces biological responses that include early-onset endothelial cell apoptosis, the production of cytokines by both host and tumor cells, as well as the induction of vasoactive compounds like NO and serotonin. The synthesis of the cytokine TNF-alpha is largely responsible for vadimezan's dramatic antitumor-antivascular effects in murine tumors and xenografts. We have shown that neoadjuvant DMXAA dramatically increases the antitumor activity of Photofrin-sensitized PDT in rodent tumor models, and have observed a similar interaction between vadimezan both HPPH and delta-aminolevulinic acid (ALA)-protoporphyrin IX-sensitized PDT. Recent experiments, in conjunction with Dr. Gollnick, suggest that vadimezan may initiate an antitumor immune response. We have recently found that vadimezan also may enhance direct photodynamic effects on the vasculature by increasing photosensitizer levels in tumor endothelial cells (with Dr. Morgan: http://classic.roswellpark.org/Site/Research/Research_Staff/Morgan_Janet_PhD). This appears to be due to vadimezan-mediated inhibition of the ABCG2 transporter that is expressed on endothelial cells and which pumps out known substrates such as the photosensitizer HPPH. In addition, we plan to study the interaction between PDT and tubulin-binding VDAs, in particular dinitrogen-substituted stilbene analogues structurally similar to combretastatin.

Select Publications

Intracellular signal transduction pathways in cancer and aging

Mikhail V. Blagosklonny, MD, PhD
Professor of Oncology

Dr. Blagosklonny is the author of over 170 research articles, reviews and book chapters. He is the Founding Editor and Editor-in-Chief of Cell Cycle and also Co-editor and co-founder of Aging and also serves as an Associate Editor for Cancer Biology & Therapy, Autophagy, Cancer Research, Cell Death and Differentiation, International Journal of Cancer, The American Journal of Pathology and PLOS ONE.

His research interests range from molecular and cellular biology to clinical investigations and specifically include oncogenes and tumor suppressors, signal transduction, cell cycle, mitosis, apoptosis, anticancer therapeutics with emphasis on translation of basic science into new anticancer strategies such as exploiting cancer cell cycling and drug resistance for selective protection of normal cells. He has extended this approach to other age-related diseases and aging itself, thus revealing an anti-aging drug to be used today (Cell Cycle, 2006, 5 : 2087-2102).

Area of General Research Interest
- Cancer biology and therapy
- Selective targeting cancer cells using drug combinations
- Mechanisms of aging and anti-aging drugs

Current Program
- Targeted combinations of anti-cancer agents and protection of normal cells
- Pharmacologic suppression of cellular and organismal aging

We have suggested that aging is not caused by molecular damage (nor by free radicals) but instead is a purposeless quasi-program driven in part by TOR (Target of Rapamycin). Theoretical analysis of cellular senescence, organismal aging, diseases of aging and effects of rapamycin reveals that rapamycin is an anti-aging drug that could be used today to slow down aging in humans and to prevent age-related diseases including cancer.
In 2009-2010, we have demonstrated that:

a. mTOR is required for cellular senescence and that rapamycin suppresses cellular senescence, by transforming it into quiescence.

b. Inhibitors of MEK and PI-3K, at non-toxic concentrations inhibit mTOR and also suppresses senescence. Therefore, certain agents, currently viewed as anti-cancer agents, could be potentially used, at low doses, as anti-aging agents.

c. Resveratrol, at concentrations that inhibit mTOR, also suppresses cellular aging.

d. Cellular aging is accompanied by pseudo-DNA damage response, which is inhibited by rapamycin.

e. p53 suppresses cellular senescence by inhibiting mTOR.

f. Rapamycin prevents age-related weight gain, decreases rate of aging, increases life span and decreases carcinogenesis in transgenic HER-2/neu cancer-prone mice. We suggest that, by slowing down organismal aging, rapamycin delays cancer.

Select Publications


Conceptual Reviews


Biology of focal adhesion kinase (FAK); Role of FAK in preventing apoptosis; Novel drugs that target FAK pathway; Other survival mechanisms of cancer cells

William Cance, MD
Surgeon-in-Chief
Chair, Department of Surgical Oncology
Professor of Oncology

Our team is focused on developing inhibitors of Focal Adhesion Kinase (FAK), a non-receptor tyrosine kinase that plays an important role in survival signaling. Our laboratory was the first group to isolate human FAK cDNA from sarcoma tissues and to show that this protein was upregulated in a wide variety of human solid tumors. Focal adhesion kinase has also been shown to be overexpressed in breast cancer tumors at early stages of tumorigenesis. Our laboratory cloned the FAK promoter and found transcription factors binding this regulatory region, including p53 and NF-KB. Our research work is currently funded by the National Cancer Institute and the Susan G. Komen Breast Cancer Foundation.

Our group is focused on isolation of novel FAK-binding proteins that interact with the N-terminal domain of FAK, such as receptor-interacting protein (RIP), p53 and NF-1. Receptor interacting protein was the first of a few FAK-interacting pro-apoptotic proteins and analysis of this interaction led to the suggestion of a possible mechanism of sequestering such proteins by FAK and providing additional survival function in the cancer cells. We used the defined FAK site of RIP binding for in silico molecular docking of small molecules from the NCI Drug Discovery Program database with the purpose to find some which disrupt the FAK-RIP complex and lead to apoptosis of cancer cells, in collaboration with Dr. David Ostrov, University of Florida.

Another binding partner in the C-terminal domain of FAK is vascular endothelial growth factor receptor, VEGFR-3. Dr. Cance’s lab has demonstrated that FAK and VEGFR-3 are important protein tyrosine kinases that physically interact and are involved in the process of tumor progression. We demonstrated that the FAK-VEGFR3 interaction provided essential survival signals for different types of cancer (breast, pancreatic and melanoma). For the first time, we have demonstrated that VEGFR-3 overexpression significantly promotes breast cancer cell proliferation, motility, survival, anchorage-independent growth and tumorigenicity in the absence of ligand expression. By computer modeling and screening of NCI small molecule database in collaboration with Dr. Ostrov (University of Florida) and biological function approaches the novel small molecule inhibitor, C4 that specifically targeted VEGFR-3-FAK interaction has been identified. The inhibitor blocked cellular viability in vitro and inhibited tumor growth of breast, melanoma and pancreatic cancers on mouse xenograft models in vivo. Dr. Elena Kurenova leads the VEGFR-3 project and collaborative study on melanoma.

Our group isolated that p53 protein as a binding partner of FAK. Targeting this interaction with peptides and small molecule inhibitors will be developed for future therapies. Computer modeling and NCI screening database isolated small molecule inhibitors targeting the FAK-p53 and FAK-Mdm-2 interactions. The model that involves targeting these protein interactions in addition to or independently of FAK-kinase function were recently discussed in a review. In addition, Dr. Vita Golubovskaya conducted a study on a novel interaction of FAK and p53, funded by Susan G/ Komen Breast Cancer Foundation. We found in collaboration with University of North Carolina a high correlation of FAK overexpression with p53 mutations in 596 breast cancer tumors that provide a basis for future targeted FAK-p53 therapy.

Finally, our group isolated a novel inhibitor of FAK, called Y15 (compound 14) that targets the main autophosphorylation site of FAK and caused breast tumor regression. The development of FAK inhibitors will be the aim of future studies for an efficient cancer therapy. Dr. Golubovskaya directs both the p53/Mdm-2 and the Y15 projects.

Select Publications

Our research focuses on identification of small organic molecules with distinctive effects on biological systems. This type of research was always in the center of drug development in the pharmaceutical industry, but over the last two decades the contribution of academic and medical institutes in this field increased dramatically.

Two main approaches to identification of bioactive molecules are rational design and screening of chemical libraries using biological readout systems. Chemical libraries are collections of different chemical compounds arranged in multi-well plates for fast and convenient high-throughput screening (HTS).

The Small Molecule Screening Core at RPCI is a state of the art, high throughput screening facility where investigators can screen the chemical libraries of more than 50,000 compounds in a variety of readout systems. Our libraries consist of over 50,000 diverse uncharacterized compounds which can be used for drug discovery and over 3,000 pharmacological and natural compounds with known activities, which can be used as a scientific research tool.

The Core provides support in all stages of screening project starting from assay optimization for HTS format, screening of compounds, and data analysis.

We also engage in collaborative efforts to develop new assay systems. One example of such collaboration is development of readout system for monitoring p53 activity in live cells undergoing stress. This assay was used in a collaborative project with Dr. Andrei Gudkov as a cell-based read-out for screening of chemical library of small molecules in a search for inhibitors of p53 activation. This work resulted in identification of the first p53 inhibitory small molecule pifithrin alpha, the first reported chemical screening study done in an academic lab. We continue studying p53 regulation and functions and participate in the development of new assays to monitor various aspects of p53 activity in normal and transformed cells.

The other examples of current or recent projects in the lab include the search for the small molecules modulators of circadian clock regulation, modulators of muscle cell differentiation and inhibitors of metastasis development.

Select publications:


11. Antoch MP, Chernov MV, Pharmacological modulators of the circadian clock as potential therapeutic drugs. Mutat Res. 2009 Nov-Dec;680(1-2);109-15. PMID: 20336820
Focal Adhesion Kinase Expression and Signaling in cancer

Vita M. Golubovskaya, PhD
Associate Professor of Oncology

The research focus is to understand the role and function of Focal Adhesion Kinase in survival pathways during tumorigenesis. Focal adhesion Kinase is overexpressed in many types of tumors and is involved in many intracellular processes: adhesion, motility, invasion, proliferation, angiogenesis and metastasis. To understand regulation of Focal Adhesion Kinase expression we have cloned promoter of Focal Adhesion Kinase and found p53 and NF-kappaB transcription factors in the regulatory sequence of promoter. One of the projects is to understand the mechanism of up-regulation of Focal Adhesion Kinase in different types of tumors. We found that p53 inhibited FAK expression through repression of FAK promoter, and analysis of 600 breast tumors with mutant p53 demonstrated high correlation between p53 mutations and FAK overexpression. In addition, we demonstrated direct interaction of FAK and p53 proteins and that FAK inhibit p53-transcriptional activity. We are studying interaction of FAK and p53 pathways. One of the projects is to target this interaction with small molecule inhibitors to decrease survival of cancer cells.

Another direction is to target Focal Adhesion Kinase autophosphorylation activity with novel small molecule inhibitors targeting autophosphorylation Y397 site. Recently, we developed novel inhibitor of FAK autophosphorylation by computer modeling, virtual screening of small molecule compounds and functional studies. This strategy has been applied to breast, pancreatic, neuroblastoma and colon cancer and we were able to decrease tumorigenesis in mice xenograft models with these FAK inhibitors. Inhibition of FAK autophosphorylation and its down-regulation with FAKsiRNA are used to reveal the function of Focal Adhesion Kinase in survival signaling, interaction with other signaling pathways, involving Src and PI3-Kinase, invasion and metastasis.

Select Publications


Cancer treatment and normal tissue protection by targeting major stress response pathways; functional screening approaches to gene and drug discovery.

Andrei V. Gudkov, PhD, DSci
Sr. Vice President of Basic Science
Professor of Oncology
Garman Family Chair in Cell Stress Biology

Andrei V. Gudkov, PhD, DSci, a pre-eminent cancer researcher was appointed Senior Vice President for Basic Research; Chair of the Department of Cell Stress Biology, and a member of the senior leadership team for National Cancer Institute (NCI) Cancer Center Support Grant at Roswell Park Cancer Institute (RPCI) in 2007. He is responsible for building on the basic and translational research strengths of the Cell Stress Biology and Drug Discovery programs. As Senior Vice President, he assists the President & CEO in developing and implementing strategic plans for new scientific programs and enhance collaborations in
research programs with regional and national academic centers as well as with industry.

Dr. Gudkov comes to Roswell Park from the Lerner Research Institute, Cleveland Clinic Foundation where he served as Chair of the Department of Molecular Genetics and professor of biochemistry at Case Western University. He earned his doctoral degree in Experimental Oncology at the Cancer Research Center, USSR and a Doctorate of Science (D.Sci) in Molecular Biology at the Moscow State University, USSR. He has authored or co-authored >160 scientific articles and holds 27 patents. He is a founder of biotech companies Cleveland BioLabs (NASDAQ, CBLI; www.cbiolabs.com), Tartis and Incuron—which develop anticancer drugs based on his discoveries.

Area of general research interest:
Discovery of novel anticancer drugs and molecular targets, development of new principles of cancer treatment and tissue protection

RESEARCH

Gudkov’s laboratory is running a broad research program involving several distinct but highly integrated branches of study. This includes identification of new disease-associated genes and deciphering molecular mechanisms of activity of their products as potential targets for therapeutic modulation by small molecules or biologics. The lab’s major focus is on developing and applying new technologies for functional gene discovery, which will lead to designing new therapeutic approaches to cancer treatment and protection of healthy tissues from cancer treatment side effects and other stresses.

Novel Gene Discovery Approaches

Gudkov’s lab pioneered functional gene discovery field by developing in mid 90s, in collaboration with Igor Roninson, one of the first gene discovery methods enabling identification of genes’ function based on gene repression, named Genetic Suppressor Element (GSE) methodology. GSE technique has resulted in discovery and/or functional characterization of a number of cancer-associated genes, including ING1, BTG2 and others (Osovskaya et al., 1996; Garkavstsev et al., 1996, 1998; Boiko et al., 2004; Komarov et al., 2008).

Selection-Subtraction Approach (SSA) is another functional genetic methodology developed in Gudkov’s lab, which allowed effective isolation of growth suppressive and killing genes and genetic elements based on negative selection (Singhi et al., 2006).

Main principles of GSE and SSA methodologies were combined to create the most powerful version of gene discovery approach named DECIHER technique. DECIHER, developed in collaboration with Cellecta, Inc (Mountain View, California; www.cellecta.com/products-services/pooled-shRNA-libraries/), involves generation and screening of diverse bar-coded shRNA libraries covering the whole transcriptome of humans and mice and enabling finding genes that control major cellular functions.

Another functional genomics approach recently developed by Gudkov’s team in collaboration with George Stark’s lab (Cleveland Clinic) is named Validation-Based Insertional Mutagenesis (VBIM). VBIM is a novel highly efficient version of retrovirus-based promoter-insertion approach that has already resulted in discovery of several new regulators of NF-kappaB signaling pathway (Lu et al., 2009, 2010).

Currently Gudkov’s lab is working on a new functional genomics-based screening methodology, which, when developed, will allow high throughput identification of biologically active secreted peptides (BASP) as a new class of prospective pharmaceuticals.

Role of p53 in Cancer and Tissue Damage

p53 studies conducted by Gudkov’s team are focused on the mechanism and role of this tumor suppressor in how normal tissues respond to genotoxic stresses associated with cancer treatment and other types of acute stresses (Garkavstsev et al., 1998; Gudkov and Komarova, 2003, 2005). Observations made in his lab in late 90s demonstrated tissue specificity of p53-mediated apoptosis and its major role in determining the radiation sensitivity of mammals (Komarova et al., 1997). This resulted in development of a paradigm-shifting strategy of pharmacological inhibition of p53 for tissue protection. It was proven by isolating a small molecule p53 inhibitor Pifithrin-a that rescues mice from lethal doses of gamma irradiation (Komarov et al., 1999). This approach, covered by a series of patents, formed the foundation for development of p53-inhibitory drugs that are currently in human trials (http://www.quarkpharma.com/qbi-en/products/QPI-102/).

Targeting various branches of p53 signaling pathway by small molecules and biologics remains one of the major aspects of Gudkov’s research. For example, a small molecule, Pifithrin-m, was isolated that blocks p53-mediated apoptosis by preventing its binding to mitochondria which acts as radioprotectant having no effect on the majority of p53 functions as transcription factor (Strom et al., 2006).

An important aspect of p53 biology discovered in Gudkov’s lab is its interaction with NF-kappaB, a signal transduction pathway, which controls inflammation and immune responses. It was found that the two major stress response mechanisms are involved in mutual negative regulation which makes p53 a general suppressor of inflammation and NF-kappaB – an oncogene (Komarova et al., 2005; Gurova et al., 2005). This finding opened a new opportunity for developing drugs capable of simultaneously targeting p53 and NF-kB; an old anti-malaria drug quinacrine was shown to belong to this category and, therefore, to act as an anticancer agent (Gurova et al., 2005).

Tissue Protecting Drugs for Cancer Treatment and Biodefense Applications

Healthy tissue protecting strategy invented and developed in Gudkov’s lab involves the use of pharmacological agents inhibiting p53 and activating NF-kappaB, thereby mimicking mechanisms acquired by tumors to escape apoptosis (Gudkov and Komarova, 2010). NF-kappaB activating approach resulted in development of a new class of drugs, named Protectans, that are derivatives of natural NF-kappaB activators produced by natural human microflora. For example, NF-kappaB-activating agent Protectan CBLB502 is a pharmacologically optimized
derivative of bacterial protein flagellin, natural agonist of Toll-like receptor pathway, which mediates mobilization of endogenous mechanisms of resistance of mammalian organisms to a variety of stresses, including lethal doses of ionizing radiation (Burdelya et al., 2008). CBLB502 is currently at advanced stages of clinical development as radioprotective antidote suitable for biodefense and radiotherapy applications.

Other Directions of Anticancer Drug Discovery: Targeting MYC, MRP1, etc.

Gudkov’s team is focused on targeting a number of other cancer treatment targets, including MYC, an oncoprotein that is essential for growth of any type of cancer, MRP1, a multidrug transporter responsible for resistance to chemotherapy of large proportion of tumors (Burkhart et al., 2008), several targets for antiviral therapies (Thakur et al., 2007; Mao et al., 2008) and others. In all of these projects, drug development is based on high throughput screening of small molecules using cell-based readout systems accompanied by comprehensive validation of specificity and followed by hit-to-lead optimization. Gudkov’s lab is especially interested in exploring opportunities for safe cancer treatment approaches which could lead to the development of new drugs for treatment childhood cancers.

Select Publications


Major goal of our lab is the discovery of new anti-cancer agents through different approaches, their testing and early stage development as well as understanding of the mechanisms of their activity. The preferred way of discovery of new compounds is through identification and genetic validation of pathways, critical for survival of different types of tumor cells, generation of cell based readout monitoring the state of a critical pathway in tumor cells and screening of small molecule libraries for compounds capable of modulation of a critical signaling pathway in a desired direction. Right now we have two parallel studies in the lab which are based on this approach. Both projects allowed discovery of active in vivo anti-tumor compounds with low toxicity profile and good perspectives of drug development. Besides this they also helped us to uncover new mechanisms of regulation of two very important pathways in tumor cells.

One project was initially focused on p53 activation by non-genotoxic stress in tumor cells with wild type but inactive p53 (1). We have isolated several compounds which activate p53, but simultaneously inhibit NF-kB in tumor cells (2). NF-kB was also found to be responsible for p53 inhibition in many different tumor types (2). These compounds bind DNA and RNA and cause profound effect on some types of transcription and translation, not being general inhibitors of transcription or translation. They also do not cause any mutagenic effect or structural modifications of DNA. Most probably they interfere with the activity of transcription elongation complexes responsible for nucleosome assembly in cells. As we believe this leads in the first turn to the inhibition of stress-related transcription and therefore hit predominantly tumor cells, which are dependent on stress signaling permanently in contrast to normal cells. We observe that NF-kB and unfolded protein response related transcription in inhibited in tumor cells treated with these compounds. We believe that this class of compounds may became a new effective and safe type of tumor therapy. Several lines of research in the lab is devoted to the testing of these compounds in the most difficult to cure cancer types, like pancreatic cancer, understanding of the compounds effect on nucleosome chaperones (FACT, HMG domain proteins) and transcription of different genes, mechanism of p53 activation and NF-kB and heat shock factor 1 repression as well as effect on other signaling pathways.

Another project was aimed on the inhibition of androgen receptor (AR) activity in androgen insensitive advanced prostate cancer (PC). We have shown that AR controls death and proliferation of PC cells on different stages, including androgen-refractory disease (3). Therefore targeting of AR may be approach for the treatment of even androgen insensitive disease. AR on this stage does not respond anymore to androgen stimulation, but is still active. It is usually mutated in ligand binding domain to accommodate stimulation by other ligands in the absence of androgens, which were depleted in the course of initial anti-androgen therapy. We generated a readout system which allows selection of compounds acting downstream of AR – ligand interactions. Several groups of compounds were isolated and tested. Some of them are very specific and potent AR inhibitors in androgen sensitive and insensitive PC in vitro and in vivo. Compounds we isolated in this screening have different mechanism of activity, one acting only against AR-dependent transactivation and others disturbing stability of AR mRNA. Experiment with these two groups of compounds allowed proposing some transcription independent role of AR in the control of PC cells survival, as well as new mechanisms of AR regulation. More detailed investigation of these questions, as well as development of anti-cancer agents based on these candidates, are the major focuses of the research in this direction.

Select Publications
Mammalian cells possess an intricate network of signal transduction pathways, which module cell behavior in response to a variety of external and internal stimuli. These cellular mechanisms normally ensure the survival of cells in specific organismal niches, as well as in conditions of temporary environmental stress. Excessive activation of these cellular mechanisms during oncogenesis contributes to enhanced survival and growth of cancer cells, modulates tumor responses to therapy and offsets the otherwise deleterious consequences of other oncogenic mutations. A better understanding of these signaling networks in health and disease are needed to identify the changes that could serve to diagnose the disease, as well as to predict its clinical properties, such as the likelihood of metastasis and the responsiveness to various therapeutic regimens. It is also needed to identify the molecules and specific molecular interactions, which could be targeted with selective toxicity against cancerous, but not normal cells. Our research in this area relies on a broad spectrum of traditional techniques of cell and molecular biology, as well as on the development of novel tools and approaches for gene discovery and characterization.

The specific signaling pathways that we have investigated include those of protein kinase B (a.k.a. Akt), NFkB, and heat shock.

Akt is frequently hyperactivated in cancers. The work of others and us has shown that this abnormality contributes to enhanced growth, reduced cell death, restructured micro-environment, and higher likelihood of additional mutations in cancer cells (Kennedy et al. 1999; Gottlob et al. 2001; Kandel et al. 2002; Somanath et al. 2007). However, non-transformed cells often respond to hyperactivation of Akt by undergoing growth arrest or differentiation, rather than oncogenic transformation. This means that cancer cells harbor additional alterations, which allow them to utilize Akt as an oncogene without arresting or differentiating, and reversal of such alterations is likely to have an anti-cancer effect. We have already identified some factors that are needed for oncogenic function of Akt (Somanath et al. 2009) and are continuing the work in this direction.

Transcription factors from NFkB family control expression of various genes that contribute to cell survival and immune response. Abnormal function of these proteins is an important factor in cancer, inflammatory and autoimmune disorders. We conducted several genetic screens for the genes whose products can control the function of NFkB, identifying both positive and negative regulators (Kandel et al. 2005; Dasgupta et al. 2008; Lu et al. 2009). We are interested in identification of additional genes with such properties, as well as in better understanding the mechanism of action of the ones that have been discovered. Our functional genetic screens utilize a new gene discovery methodology, which is based on improved insertional mutagenesis (Kandel and Stark 2003; Kandel et al. 2005). We are working on enhancing the technical aspects of this approach, including increasing the throughput of identification and validation of relevant genes and extending this approach to in vivo gene discovery applications.

We were part of the team that had identified a novel RNA molecule, which modulates the response of mammalian cell to thermal stress (Shamovsky et al. 2006). This was one of the first examples of a non-coding RNA that is a structural element of mammalian signal transduction. Our interest in the role of non-coding RNAs in signal transduction continues in the ongoing work on microRNAs, which have emerged as the major class of regulators of various cellular processes (reviewed in (Gartel and Kandel 2006; Gartel and Kandel 2008)).

We heavily rely on retroviruses as tools for gene delivery and gene discovery. This fuels our interest in the properties of these viruses and led to the finding of a new mechanism of emergence of recombinant retroviruses (Kandel and Nuplier 2002) and the interaction between the viral vectors and a newly discovered human virus (Dong et al. 2008).

Select Publications
Biomolecular Resources: Proteomics, Mass Spectrometry, DNA Sequencing and NMR Spectroscopy; Research Interests: Proteomics, Metabolomics and Imaging Mass Spectrometry

A. Latif Kazim, PhD
Director, Biomolecular Resource Facility
Associate Professor of Oncology

EDUCATION

Boston University, Boston, MA, BA, 1971, Chemistry/Biology
University of Minnesota/ Mayo Medical School, Rochester, MN, PhD, 1979, Biochemistry/Immunology
Mayo Medical School, Rochester, MN, Postdoctoral Fellowship, 1979-1981, Immunology

Biomolecular Resource Facility and General Research Interests

The Biomolecular Resource Facility is a core laboratory that provides advice and technical assistance to institute staff in DNA sequencing, genotyping, mass spectrometry, proteomics, and nuclear magnetic resonance spectroscopy. The main objectives of the facility are to assess the technical needs of the staff in the context of these analytical methods, and develop resources to assist investigators in accomplishing their research goals.

Research and developmental interests in this laboratory currently focus on structure/activity relationships in proteins and peptides, and the use of mass spectrometry-based methods in studying the effects of oxidative stress on DNA and proteins, metabolomics and tissue imaging by mass spectrometry.

Heat Shock Proteins are known to play essential roles in normal cellular functions and are involved in numerous pathways involving protein processing and interactions. In collaboration with Dr. John Subjeck, we employed a grp170-secreting tumor cell system to determine whether tumor cells engineered to secrete grp170 generate an anti-tumor specific immune response. Further, we examined the possibility that secreted grp170 can bind to and co-transport out of tumor cells full-length tumor antigens that may play a role in the anti-tumor immune response. Immunization of animals with grp170-secreting tumor cells results in rejection of the tumor by induction of antigen-specific, CD8-dependent immune responses. The secreted grp170 was able to deliver full-length tumor antigens to the tumor microenvironment, thus making them available for uptake by antigen presenting cells (APCs) to initiate tumor-specific immune responses. These data paralleled earlier studies showing that hsp110 or grp170 are able to chaperone full-length proteins, and when complexed with protein antigens and used as vaccines, these complexes elicit immune responses in vivo against the protein antigens. This cell-based approach has the potential to be utilized as a tumor-specific vaccine in tumors of various histological origins.

A recent research interest of the laboratory is in the area of imaging mass spectrometry (IMS) – the use of mass spectrometric methods to "image" analytes such as drugs and metabolites in tissue sections. Tissue imaging is a promising technique as it allows the determination of the distribution patterns derived from drug treatment (precursor drug and metabolites) in specific tissues, and at a lateral resolution ranging from 100 μ (MALDI) to ~3 μ or less (TOF-SIMS). In collaboration with Dr. Mari Prieto at Thermo-Fisher Scientific, using a MALDI source and an ion-trap mass spectrometer for IMS we recently identified and confirmed most of the known metabolites of irinotecan in liver and tumor tissues obtained from mice treated with this drug. Additional experiments are underway to determine whether the distribution of the drug and metabolites are related to the vascularity of the tumor. In related studies and in collaboration with Dr. Youcef Rustum of RPCI and Dr. Joseph Gardella at the University at Buffalo we have used time-of-flight secondary ion mass spectrometry (TOF-SIMS) to determine the spatial distribution of metabolites of methylselenocysteine (MSC) in liver and in Xenografts of human tumor tissues, demonstrating that the metabolites were in direct proximity to the vasculature. MSC and other selenium compounds have been utilized by the Rustum laboratory in cancer chemotherapy regimens to enhance the efficacy of chemotherapeutic drugs. The mechanism by which this enhanced efficacy occurs is unknown. The results from IMS show that MSC metabolites are localized to the vasculature of tumor and liver tissue, which may result in a more effective delivery of chemotherapeutic agents into the tumor.

Select Publications


4. Protein complexes of Focal Adhesion Kinase as the targets in tumor growth, angiogenesis and metastasis.

Protein complexes of Focal Adhesion Kinase as the targets in tumor growth, angiogenesis and metastasis.

Elena V. Kurenova, PhD
Associate Professor of Oncology

My research is focused on Focal Adhesion Kinase (FAK) - tyrosine kinase that functions as a key orchestrator of signals leading to survival of cancer cells, invasion and metastasis. FAK interacts with a number of critical proteins involved in survival signaling in cancer cells, some of which were discovered by phage display approach. We hypothesized that targeting a protein-protein interface with drug-like small molecules is a feasible strategy for inhibiting tumor growth. We aim to elucidate the mechanisms of these FAK-related survival signals and develop novel therapeutic to inhibit this signaling in human tumors. We selected small molecules that disrupt some protein-protein interaction of FAK and cause cancer cell death in vitro and in vivo.

We have shown that serine/threonine kinase RIP - a major component of the death receptor complex, binds to FAK. We hypothesize that this interaction is a critical component for suppressing apoptosis in tumor cells. We are focused on understanding the mechanism of FAK-RIP interaction and signaling which may provide a molecular basis for the development of new cancer therapeutics.

FAK and VEGFR-3 are tyrosine kinases that have been identified as critical signaling molecules not only for survival of cancer cells, but also important in vascular development. Previously we have shown that VEGFR-3 and FAK physically interact and are overexpressed in cancer cells to provide a significant survival advantage for the tumor cells. We subsequently identified a novel small molecule inhibitor that targeted VEGFR-3-FAK site of interaction and disrupted the survival function of these two proteins. We utilized the crystal structure of the FAK focal adhesion targeting (FAT) domain for molecular docking of small molecules that targeted the VEGFR-3 binding site on FAK. We identified a small molecule C4 that disrupted VEGFR-3-FAK binding. In vitro testing of this compound resulted in the selective growth inhibition, reduction in motility and invasion, and induction of apoptosis in a time- and dose-dependent manner in many cancer cell lines, especially those that overexpressed VEGFR-3. In vivo, C4 showed a marked reduction of tumor growth and was synergistic with doxorubicin chemotherapy in breast cancer xenograft models, with dacarbazine in melanoma xenograft models, and with gemcitabine in pancreatic cancer xenograft models. These results demonstrate that targeting the FAK-VEGFR-3 interaction with small molecules inhibited the survival function of these two tyrosine kinases, representing a unique approach for molecular-targeted highly-specific cancer therapeutics. Now we aim to elucidate the effect of this inhibition on blood and lymphatic vasculature of the tumor and tumor metastasis.

Select Publications


5. Golubovskaya V, Finch R, Zheng M, Kurenova EV, Cancé WG. 2008 The 7 amino-acid site in the proline-rich region of the N-terminal domain of p53 is involved in interaction with FAK and is critical for p53 functioning. Biochem J., 411(1):151-60


Malignant tumors of childhood represent an uncommon heterogeneous group of neoplasms originating from virtually any anatomical structure. Despite major improvement through the integrated, multimodality treatment approach including combination chemotherapy, childhood cancer remains the leading cause of disease-related death in children. Moreover, recently approved chemotherapeutic agents that have significant antitumor activity in adult cancers appear to be inactive in conventional therapy performed in children with aggressive and recurrent cancers. The prevailing explanation for the development of cancer over the past 50 years has raised the notion that apparently cancers represent the failure of the tumor cells to differentiate along a pathway that would be expected for their tissue of origin. Hence, investigation of the mechanism about the underlying molecular defect in cancer cells to differentiate would be important to develop new biologically based treatment approach in making bad cells go good.

A aberrant gene function and alteration in epigenetic regulation of gene expression are now increasingly recognized to cause differentiation dysregulation in cancer development and progression.

Our research program is focused on basic and translational research that connects the normal skeletal muscle differentiation program and its dysregulation in the development of childhood rhabdomyosarcoma (RMS). Our laboratory pursues two major research programs: Epigenetic gene regulation and Drug discovery.

The epigenetic gene regulation program involves deciphering the epigenetic mechanism as potential target strategy for therapy. This program is aimed to identify the epigenetic modifiers regulating normal and perturb skeletal muscle differentiation. Particularly, the research focuses on epigenetic modulation of gene expression regulating skeletal muscle transcription in model system and in rhabdomyosarcoma (RMS).

The drug discovery program involves searching small molecule pharmaceuticals capable of activating muscle differentiation program in rhabdomyosarcoma for the treatment of childhood rhabdomyosarcoma.

The ultimate goal of both research programs is aimed to develop biologically based approach for the invention of differentiating agents as new anti-rhabdomyosarcoma pharmaceuticals.

**ONGOING RESEARCH PROJECTS:**

**Epigenetic mechanism regulating skeletal muscle differentiation transcription**

Our laboratory has discovered that epigenetic modifier histone H3-lysine 9 methyltransferase Suv39h represses muscle gene expression in executing muscle differentiation. We are studying the mechanism of Suv39h mediated epigenetic events in arresting muscle cell differentiation and the balance between histone H3-lysine 9 methylation by Suv39h and demethylation of this epigenetic repressive mark in regulating myogenic transcription during muscle differentiation.

**Epigenetic mechanism regulating rhabdomyosarcoma development**

Rhabdomyosarcoma is a childhood malignant tumor comprising 5-8% of all cases of cancer in children and thought to arise due to arrest of muscle differentiation program despite the expression of MyoD that acts as a key myogenic transcriptional regulator of the muscle differentiation. We are investigating the epigenetic mechanism that is encountered in the failure of MyoD-mediated differentiation in rhabdomyosarcoma. In addition, we are investigating the potential contribution of oncogenic fusion protein Pax3-Fkhr, a genetic signature in aggressive alveolar rhabdomyosarcoma (ARMS) development, mediating epigenetic alteration in the defect of muscle differentiation program in these tumor cells.

**Identification of small molecule modulators by screening chemical library**

This research program involves the identification of small molecule modulators in biological readout systems targeting myogenic regulator MyoD, epigenetic modifier Suv39h and oncogenic fusion protein Pax3-Fkhr capable of inducing muscle differentiation program in rhabdomyosarcoma.

**Select Publications**


Surgery, chemotherapy and radiation medicine are three modalities which are used, often together, in the management of cancer. Therapeutic Medical Physics is an applied branch of physics which is associated with the application of physics to radiation medicine so that delivery of ionizing radiation to a patient is safely and accurately targeted to the tumor. Accordingly, the research in this field is very rewarding personally as the results and the benefits to society are usually immediate. Besides, providing clinical physics care to all patients undergoing treatment at the institute, half a dozen medical physicists in the department of Radiation Medicine of Roswell Park Cancer Institute, also pool together their knowledge and expertise in advancing scientific research in this field often even collaborating with professionals from other fields like physics, computer science, etc. not to mention our clinical colleagues. At any given moment of time, there are various research projects in various stages of completion in the department.

Brachytherapy plays an important role in the treatment of female gynecological cancers. A good part of the century long clinical experience has come from use of a tandem and ovoid applicator set which has tungsten shields in it to minimize the radiation dose and hence radiation toxicity to the nearby critical structures, rectum and bladder. Unfortunately due to practical limitations, the dose reduction due to their presence was ignored and hence the clinical experience gained relies on incorrect recorded dosage to these two vital organs. Thus the published tolerance values in literature for these structures can not be used for new set of CT/MR compatible applicators which can not have any shielding due to imaging artifacts. We are presently developing experimental methods to determine the difference in the recorded and actual radiation dosage to these organs using various detectors. This study will provide guidance to properly apply corrected constraints for rectum and bladder using CT/MR applicators.

Project 2 is based on collaboration with researchers in Carestream Health, Rochester, NY. We have successfully demonstrated a novel algorithm to use Electronic Portal Imaging Detector (EPID) to track the lung tumor in real time without requiring any external surrogate. It is very promising field which one day may help us to gate the treatments of lung patients using this technique which will be simple and yet free of less accurate external surrogates. This will also result in the reduction in tumor margin commonly employed for lung cases resulting in lower radiation toxicity to these patients.

In radiation therapy, it is very important to accurately reproduce the patient position during treatment as was used during treatment simulation. This is presently carried out using the technical information recorded manually during simulation. In another project, we are seeing the feasibility of using digital cameras along with information extracted from the patients treatment plan to verify that the patients is not only in its right position before the treatment is started but also to continuously track and monitor the patients’ position during his/her entire treatment. Our initial results are very promising in this study.

In yet another project, we are trying to find optimal beam arrangements and their mathematical characteristics to achieve an optimal treatment plan which best satisfies clinical constraints using a super computer at CCR, UB. We have already demonstrated the proof of concept in which patient specific images along with appropriate image segmentations and desired clinical constraints are fed to a cluster of computers at CCR where hundreds of combinations are tried using a process called Genetic Algorithm to come to an optimal solution. The process has been successfully demonstrated for 3D conformal therapy and we wish to extend it for intensity modulated radiotherapy (IMRT) in near future as well.

Select Publications:


Mechanisms and enhancement of Photodynamic Therapy in cancer and cancer stem cells

Janet Morgan, PhD
Clinical Assistant Professor of Oncology

My research interests lie primarily in the field of photobiology and photodynamic therapy (PDT) a treatment for cancer and other diseases in which photosensitive drugs are activated by light to destroy malignant or other target tissue. Currently approved photosensitizing drugs for PDT are not optimally selective and do not readily penetrate tissue. In addition, heterogeneity of tumors and of photosensitizer distribution, may affect the response. To be most effective, a selective tumor response is required with minimal side effects.

To achieve this goal, we use several in vitro and in vivo models, and examine the effects of photosensitizers, their distribution and phototoxic mechanisms by different approaches including photoreactivity, biochemistry, molecular biology and fluorescence imaging.

In particular we are interested in targets and mechanisms of PDT toxicity a) to understand the mechanisms by which the PDT response is effected from the whole animal response to the tissue, cellular, subcellular and molecular levels b) to aid in designing and synthesizing more efficacious drugs and delivery systems for photodynamic therapy and c) to help to optimize PDT protocols, and their effectiveness.

Our current focus is using small drug molecules which interfere with or inhibit mechanisms and pathways which control cancer growth, survival and proliferation and which may enable us to enhance the PDT response by using combination therapies. In particular stem cell-like cancer cells PDT have properties which may help them to evade PDT toxicity including the expression of pumps which efflux photosensitizers, and innate resistance to oxidative stresses. Also, targets at or within the mitochondria define critical sites of photosensitizer uptake, synthesis from prodrugs, binding and damage. Some of the binding sites we are examining include the peripheral (mitochondrial) benzodiazepine receptor (PBR), which is expressed at high level in tumors and which may help to concentrate photosensitizers in mitochondria. The PBR is a potential sensitive site for PDT and the role of its natural ligands in enhancing photosensitizer uptake and enhancement of reactive oxidative species is under investigation.

Select publications

Computational methods are now playing a larger role than ever in all aspects of science, including the diagnosis and treatment of disease. No other technology has seen such tremendous advances in the last half century as computer technology. The exponential advances in computer power make it critically important to understand its potential, and leverage its capabilities in our fight against cancer. As a medical physicist, I am interested in applying computational techniques to problems in radiation medicine.

A large and promising branch of computation is optimization, or techniques for selecting values of independent variables that maximize or minimize a particular parameter, or goal. In radiation oncology, there is the goal of maximizing the radiation dose delivered to the tumor region, while at the same time minimizing the dose absorbed by healthy tissue. This is accomplished by varying the independent parameters (such as radiation beam energy, intensity, shape, and delivery geometry) of a treatment plan.

One exciting clinical treatment modality that incorporates these ideas is intensity modulated radiation therapy, or IMRT. Our recent work has focused on applying principles of computation to the optimization of patient-specific parameters in IMRT. We have explored promising optimization techniques, such as the genetic algorithm, which is based on ideas from biological evolution. These methods become even more powerful when implemented in a distributed-computing framework. To this end, we have formed a collaboration with the Center for Computational Research (CCR), an academic supercomputing center that forms part of UB’s Center for Excellence. By employing the CCR’s computational resources, we have applied the genetic algorithm to improve IMRT treatment plans.

Another project involving optimization addresses the patient setup problem: how do we best position a patient for a complex radiation treatment, ensuring that he or she is in the correct 3D location and orientation? We are investigating a novel approach to this problem, by using optical information obtained from a regular digital camera, and applying optimization techniques to determine the 3D geometric parameters accurately. This method will allow us to improve patient setup without subjecting the patient to increased ionizing radiation exposure.

Select Publications:


Molecula r mechan isms of transformation and senescence

Mikhail A. Nikiforov, PhD
Associate Professor of Oncology

Dr. Nikiforov joined the staff of Roswell Park Cancer Institute in 2007. He completed his PhD in Genetics at the University of Illinois at Chicago, IL after receiving his masters and bachelor’s degree in Biochemistry from Moscow State University, Moscow, Russia.

Dr. Nikiforov completed his postdoctoral fellowships at the University of Rochester and Princeton University and since 2004 worked as an Assistant Professor in the Department of Dermatology at the University of Michigan. He is a member of the American Association for Cancer Research and Society for Investigative Dermatology.

Research Interests

Molecular mechanisms of oncogene-mediated transformation and senescence of melanocytic cells. Role of nucleotide metabolism in oncogenic transformation, genomic instability and senescence. Mechanisms regulating stability of the oncoprotein C-MYC in melanocytic cells.
Multifunctional Agents for Imaging and Therapy

Ravindra K. Pandey, PhD
Distinguished Professor of Oncology

Dr. Pandey was awarded PhD in medicinal chemistry from the University of Rajasthan, Jaipur, India. He then worked as a postdoctoral fellow and research associate in the laboratories of Professor Kevin M. Smith (University of California, Davis, 1980-1983 and 1984-1986) and the late Professor A. H. Jackson (University College Cardiff, Wales, 1983-1984) on the chemistry and biochemistry aspects of porphyrin-based compounds. He joined Oncologic Foundation of Buffalo in 1986 and was involved in a photodynamic therapy (PDT) project related to Photofrin® funded by Johnson & Johnson. In 1990 he left the Foundation and joined the Photodynamic Therapy Center, Roswell Park Cancer Institute, Buffalo, where he is currently associated as Distinguished Professor and Director of Pharmaceutical Chemistry, Department of Cell Stress Biology. He also has an appointment as Professor with the Institute of Lasers, Photonics and Biophotonics, SUNY at Buffalo.

Description of Research:
Photosensitizers for Photodynamic Therapy: For the last several years one of the objectives of Dr. Pandey's laboratory has been to synthesize and evaluate tumor-avid porphyrin-based photosensitizers for photodynamic therapy (PDT) exhibiting the long wavelength absorption in the range of 660-800 nm. Such compounds on exposing to light at appropriate wavelengths convert the molecular oxygen present in tumors to singlet oxygen, a cytotoxic agent responsible for the destruction of tumors. Starting from chlorophyll-a and bacteriochlorophyll-a, his group synthesized and evaluated a series of photosensitizers. On the basis of SAR and QSAR studies conducted in a highly stimulating collaboration with other members of the PDT group of our department, Dr. Pandey's group has been able to select the best candidate from each series, and these photosensitizers are currently at various stages of clinical (Phase I/II) and preclinical trials.

Molecular Modeling-Based Target-Specific Photosensitizers: The major challenge of cancer therapy is the selective destruction of malignant cells while sparing normal tissue. While certain photosensitizers show a degree of selectivity, the parameters chosen for treatment in patients are limited by reactions of the normal tissue within the light field. Therefore, one of the objectives of Dr. Pandey's research program has been to improve and optimize PDT by targeting photosensitizers to tumors. His current approach is to target the photosensitizers to integrins (avb3), folate receptors and certain cellular carbohydrate receptors (e.g. galectins) over-expressed in a variety of malignant tumors. Dr. Pandey’s group is using molecular modeling-based approach for designing target-specific photosensitizers in collaboration.

Multifunctional Tumor-Imaging (MRI, PET and Fluorescence) and Therapeutic Agents: In recent years, cellular and molecular biology have ushered in a new era for the characterization of the tumor tissue at the molecular level. The non-invasive molecular imaging of the specific type of tumors in vivo followed by tailored medical intervention is becoming the new frontier of cancer treatment. Therefore, for investigating the utility of tumor-avid photosensitizers as vehicles to deliver the imaging agents (MRI, Nuclear Imaging, Optical Imaging) to tumors, HPPH (a chlorophyll-a analog developed in our laboratory currently in Phase I/II human clinical trials) was conjugated with a variety of imaging agents. In preliminary studies, the corresponding conjugates e.g., HPPH-DTPA, was found to be a promising dual function (tumor MR imaging and therapy) agent. This approach is now being extended for developing target-specific agents for improved efficacy.

PDT and Nanotechnology: In collaboration with the Biophotonics group at SUNY Buffalo, and Dr. Kopelman, University of Michigan, Dr. Pandey's group has initiated several research project focused on investigating the utility of nanotechnology platforms (Ormosil, gold and polyacrylamide) in developing multifunctional nano-platforms for tumor imaging and phototherapy. These nanoconstructs also provide an opportunity to introduce tumor-targeting moieties at the peripheral position of the nanoparticles.
Select Publications (from a list of 250 publications)


Applications of Medical Physics to Cancer Diagnosis and Treatment
Matthew B. Podgorsak, PhD, DABMP, FAAPM
Associate Professor of Oncology

Medical Physics is an applied branch of physics that is concerned with the application of physical concepts and methods to the diagnosis and treatment of disease. Medical physicists provide clinical services and are involved in research in any of the four subfields of medical physics: therapeutic radiological physics, diagnostic radiological physics, medical nuclear physics, and medical health physics. At Roswell Park Cancer Institute, the medical physics division is primarily interested in research aimed at improving the delivery of radiation therapy to patients, although we do collaborate with medical physicists at other facilities that are involved in the other branches of medical physics. We also collaborate with scientists in other fields, such as physics, engineering, chemistry, computer science, and biology, with whom we share a common interest.

Research in a typical medical physics laboratory is either applied in nature or it is initially theoretical but is quickly translated to clinical practice. Currently, research under my direction is focused on three main themes: delivery of radiation therapy using state-of-the-art techniques, development of models to predict tumor motion during a patient’s respiratory cycle, and enhancement of quality assurance techniques for our department’s clinical services. Implicit in all research is an overarching interest in process development in order to ensure patient safety during state-of-the-art clinical treatment delivery.

The Department of Radiation Medicine has recently acquired two new clinical linear accelerators equipped with image guidance enabling very precise and accurate dose delivery. One delivery technique is known as volumetric modulated arc therapy (VMAT), and we have been involved in research aimed at identifying the anatomies that are best treated with this new approach. Early indications suggest that VMAT is a very powerful tool that provides clinical benefit to many patients, however, there is nonetheless a subset of patients for whom VMAT is not appropriate. We are currently in the process of identifying this sub-group of patients through treatment plan simulations and enhanced dose calculations coupled with empirical measurement.

The second theme is based on collaboration with colleagues in the Department of Mechanical and Aerospace Engineering at UB. We are developing models that will hopefully successfully predict the excursion of tumors within a patient’s thoracic cavity during respiration. Applications of these models during radiation therapy treatment planning for lung tumors may enable us to minimize the size of radiation beams with an anticipated decrease in treatment related side effects.

The research project satisfying the third theme has been ongoing for several years and is based on optimization of quality assurance techniques used to ensure safe and accurate dose delivery. We have recently developed a mathematical algorithm that has been applied to patient-specific quality assurance measurements of intensity modulated radiation beams, and we are in the process of expanding the model to VMAT delivery. It is expected that research along the quality assurance theme will continue indefinitely. The need for safety in clinical care will always be present, and as new treatment techniques and paradigms are introduced it will be necessary to develop new quality assurance tests, equipment, and programs to ensure safe delivery of care.

Select Publications:


Nanoparticle drug formulation and tumor microenvironment

Arindam Sen, PhD
Assistant Professor of Oncology

EDUCATION
BSc, Physics, Delhi University, Delhi, India
MSc, Physics, Delhi University, Delhi, India
PhD, Life Sciences, J. Nehru University, N. Delhi, India
Postdoctoral, Biophysics, Chelsea College, University of London, London, UK

Research Interest
My general research interests include structure-function relationship of biological membranes, model membrane systems and biomolecules using biophysical techniques including microscopy, spectroscopy, x-ray and electron diffraction. My specialization is in the area of electron, optical and atomic force microscopy and, uv/vis and infrared spectroscopic techniques. Specific interests include developing strategies for parenteral drug delivery including transdermal, lipidic nanoparticles and macromolecular assemblies as drug delivery systems. Further, we are investigating the physical barriers posed by the tumor microenvironment on effective chemo and radiation therapy, and possible approaches for overcoming those barriers.

CURRENT RESEARCH
Transdermal Drug Delivery and Analyte Monitoring
The broad aim of this program is to develop technologies that can automate transdermal drug delivery and analyte monitoring with minimal discomfort and inconvenience. Recent transdermal electroporation work in this laboratory has resulted in a novel method using electric pulses and lipid formulations to achieve a transient increase in skin permeability, enabling sampling of systemic glucose and delivery of insulin. We have received an US patent for transdermal monitoring of analytes and have a patent pending for transdermal delivery.

Lipidic Nanoparticles for Drug Delivery
The aim of this program is to design and test novel lipidic nanoparticles for drug delivery to tumors with the aim of translating this program to the clinic. Amongst the lipidic nanoparticles that we have tested include those that are temperature sensitive for which we have received an US patent. Research is aimed at tumor targeting of nanoparticles by using hyperthermia and other adjuvant therapies to enhance the therapeutic efficacy in difficult to treat solid tumors including metastatic cancers.

Tumor Microenvironment
The aim of this program is to examine changes in the tumor vasculature and microenvironment in response to hyperthermia or other therapies that can influence tumor drug delivery. Our aim is to establish role of different adjuvant treatments like hyperthermia in increasing tumor uptake of drugs possibly by remodeling tumor vasculature and/or by inducing changes in tumor hydrostatic pressure.

Patents

Select Publications
Cancer Imaging/Targeted Therapies

Mukund Seshadri, DDS, PhD
Co-Director, Preclinical Imaging Facility
Assistant Professor of Oncology

Research program
My research program is focused on the use of advanced imaging techniques such as magnetic resonance imaging (MRI) and optical molecular imaging techniques in preclinical and clinical studies to assess the biological characteristics of tumors and their response to traditional and novel anticancer treatments.

The program is also focused on the development of novel multifunctional and multimodal (MRI and optical imaging) nanoparticles for targeted imaging and therapy through active inter- and intradepartmental collaborations at Roswell Park and the University at Buffalo.

We have previously demonstrated the potential of targeting angiogenesis for therapeutic benefit in head and neck squamous cell carcinomas (HNSCC), gliomas, colorectal cancers. Using MRI, we have successfully characterized the vascular response of tumors to antiangiogenic, antivascular and chemopreventive agents such as selenium and vitamin D in head and neck, colon, lung and prostate cancers. We are currently focused on developing non-invasive imaging based early response biomarkers that can reliably predict therapeutic outcome in HNSCC xenografts derived from primary human tumors. Studies are also focused on the development of MR contrast agents and imaging techniques for the detection of metastatic disease in animal models of head and neck and colon cancer.

Select Publications

Magnetic resonance imaging in animal models of disease

Joseph Sperryak, PhD
Co-Director, Preclinical Imaging Facility
Imaging Research Scientist

Dr. Sperryak has been involved in a broad range of research projects incorporating the use of magnetic resonance imaging (MRI) for studying small animal model of disease. His recent interests have focused primarily in three areas, a) development and assessment of novel MRI/PDT contrast agents for the purpose of combining imaging and therapy within a single compound, b) use of MRI to non-invasively characterize changes in tumor microvasculature arising from anti-cancer therapies, and c) application of balanced, steady-state free precession imaging for efficient and accurate measurement of tissue MR relaxation rates.

Collaborating with Dr. Ravindra Pandey (Cell Stress Biology), our lab has been developing and characterizing novel, multi-functional imaging agents for use in both imaging and photodynamic therapy (PDT). Combining imaging capabilities with a tumor-specific therapeutic has multiple advantages, including improved tumor boundary delineation and non-invasive tracking of tumor uptake and pharmacokinetics. These capabilities may lead to improved prognostic indicators on the efficacy of PDT treatment based upon imaging biomarkers.

Dynamic-contrast enhanced MR imaging is being utilized to probe changes in vascular function as a result of chemotherapy (e.g. doxorubicin) or biophysical therapies such as PDT or whole body hyperthermia. The microvasculature architecture within tumors differs from normal vasculature in a number of ways. Tumor vasculature is chaotic and hyper-permeable, often exhibiting reduced blood flow, which in turn can reduce the efficacy of anti-cancer treatments. Using MRI, changes in tumor blood flow and vascular function can be studied in situ, leading to greater understanding of the vascular effects of such treatments and potentially to better outcomes.

Critical to this work is the ability to perform rapid measurement of tissue relaxation rates in vivo with a high degree of accuracy and sensitivity. Balanced, steady-state free precession (bSSFP)
imaging is being explored in a preclinical environment as a means of rapid relaxometry, as it offers many advantages over alternative methods, namely a) high signal to noise ratios, b) improved spatial homogeneity over a large volume, c) short acquisition times, and d) simultaneous extraction of both T1 and T2 relaxation rates within a single MRI dataset. This methodology is currently being applied for use in novel contrast agent development, microvascular assessment, and high-resolution in vivo microscopy.

Select Publications:


Oncology drugs as a therapeutic class tend to have the lowest therapeutic index of any drugs in widespread clinical use, based on their antitumor efficacy vs. toxicity to the patient. Our long term objective is to employ drug carrier technology to mitigate drug toxicity, increase antitumor potency, or overcome drug physicochemical, pharmaceutical, or biodispositional shortcomings. The three main foci of our lab are to (i) develop new carrier-based formulations that have specific properties that could improve the therapeutic utility of specific drugs, (ii) investigate the mechanisms by which carrier incorporation of drugs can change the ‘apparent pharmacology’ and confer upon the drug/carrier complexes new mechanisms of antitumor effect that would not be predicted from the mechanism of action of the drug itself, and (iii) develop a rational, mechanistic, and quantitative basis upon which to combine drug carrier -based formulations with conventional cytotoxics or novel target-selective agents.

In terms of the development of new carrier-based anticancer drug formulations, our group was the first to elucidate the physicochemical basis for designing stable, liposome-based formulations containing taxanes such as paclitaxel, the active agent in Taxol®. These formulations eliminated the toxic co-solvent in which this poorly-soluble drug was administered to patients, and in addition showed significantly reduced toxicity to critical normal tissues. Our most recent publication on taxane-containing liposomes showed that in a drug-resistant, intracranial rat brain tumor model, paclitaxel showed activity superior to the clinical standard (1). Mechanistic studies that employed quantitative, systems-level modeling of antitumor pharmacodynamic effects that were observed by using magnetic resonance imaging, which provided repeated, non-invasive measurement of tumor volume progression, demonstrated that the enhanced antitumor efficacy of the liposome formulation resulted not only from its reduced toxicity, but also from a greater propensity to exert a tumor ‘priming’ effect. Other groups have shown that an initial administration of taxanes creates a defined temporal window in which a subsequent dose undergoes greater deposition. Our group demonstrated that in this drug resistant rat brain tumor model, the taxane clinical standard showed no priming effect, whereas with the liposome-based formulation, a pharmacodynamic model that hypothesized a priming effect best captured the effect of varying taxane liposome dose and schedule of administration (1).
continues to explore the strengths and limitations of different types of semi-mechanistic models in terms of describing antitumor drug action quantitatively (2,3).

The necessity to acquire experimental data that enables development and testing of these novel pharmacokinetic/pharmacodynamic models often challenges existing analytical technology. A long-standing effort of our group is to develop ultra-sensitive approaches for drug quantification in the small samples that are obtainable in animal model systems (4).

The laboratory also investigates other types of carrier-based antitumor drug formulations that have distinct properties. Our group was the first to demonstrate that an FDA-approved nanoparticulate formulation, consisting of doxorubicin encapsulated in highly-stable, long-circulating liposomes, could exert a profound ‘anti-vascular’ effect in the intracranial rat brain tumor model. When administered on a specific schedule, the doxorubicin-liposome formulation compromised tumor vascular permeability, which permitted greater deposition of subsequent doses. A recent publication demonstrated that the amount of drug deposited in tumor doubled on the second administration, as a result of the vascular compromise (5). This effect is not observed with the free drug. An upcoming publication provides evidence that the nanoparticulate doxorubicin formulation exerts these novel antivascular effects by extravasation and sequestration near the tumor blood vessel wall. This creates an intra-tumor depot that kills tumor vascular endothelium over time, resulting in higher tumor perfusion and permeability of the tumor vasculature. These studies also suggest that the antivascular effect of nanoparticulate doxorubicin formulations could be exploited to increase tumor deposition of other, conventional antitumor drugs, thus overcoming the barrier of the tumor vasculature to achieving drug levels within tumors that are sufficient to reverse tumor progression.

Select Publications:
Select Publications:


