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COLUMBIA UNIVERSITY
CENTER FOR RADIOLOGICAL RESEARCH

THE CENTER FOR
RADIOLOGICAL
RESEARCH

2019
ANNUAL
REPORT



CRR 2018 FACULTY AND RESEARCH STAFF



COLUMBIA

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CENTER FOR RADIOLOGICAL RESEARCH



Our mission is to be on the forefront of radiological science and its applications in clinical medicine, public health, and national defense.

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NOTE FROM THE DIRECTORS



David J. Brenner, PhD, DSc

It continues to be an honor and privilege to lead the Columbia University Center for Radiological Research (CRR). For more than a century, the CRR has been a premier institution in radiation science and has led pioneering research into the biological effects of radiation. Our guiding mission is to be on the forefront of radiological science and its applications in clinical medicine, public health, and national defense.

We would like to thank you for your support and reflect on some of the exciting research we conducted in 2019, including efforts to improve radiotherapy of prostate cancer; ongoing research on radiation biodosimetry and the development of agents for the mitigation of acute or late radiation effects; and efficacy and safety testing of the Differential Ultra-Violet Sterilizer, a cost-effective technology we developed that uses UV light to kill drug-resistant bacteria. These are just a few of our exciting research projects in 2019, which you will read more about in the report.



Tom K. Hei, PhD

We are also thrilled to share what we have on the horizon—an exciting new project called FLASH radiotherapy that involves the ultra-fast delivery of radiotherapy treatment. Our goal is to understand how FLASH radiotherapy kills cancer cells while leaving nearby healthy tissue intact. In addition to FLASH radiotherapy, in early fall 2020 a booster linear accelerator (LINAC) will be installed at Columbia's Radiological Research Accelerator Facility (RARAF), which will enable us to study heavy-ion radiation, a promising new form of radiation therapy.

We are grateful to the CRR team and the CRR Advisory Council for all of the exciting developments we made over the past year. We are extremely proud of these accomplishments, and with your help we hope to achieve even more.

Sincerely,

DAVID J. BRENNER, PHD, DSC

TOM K. HEI, PHD

NOTE FROM THE DEPARTMENT CHAIR



I am delighted to serve as chair of the Department of Radiation Oncology at Columbia University Vagelos College of Physicians where I can help build and support one of the largest and oldest radiation research centers in the nation, the Columbia University Center for Radiological Research (CRR).

Before arriving at Columbia, I was chair of the Department of Radiation Oncology at the Vanderbilt University School of Medicine. As a physician scientist, my focus has long been on transforming the standard of care for cancer patients through research and innovation. In my current role, I aim to strengthen the bridge between the CRR's groundbreaking research in radiation science and clinical care in order to deliver the most effective cancer therapies. Towards this goal, physician scientists across the Department of Radiation Oncology, including Drs. Fred Wu, Eileen Connolly, and Simon Cheng, are working collaboratively with CRR investigators on some of the research projects highlighted in this report.

In addition to promoting clinical excellence, technological innovation, and patient-centered research, I look forward to recruiting and mentoring the nation's leading experts in radiation science. My goal is to ensure that Columbia's radiation oncology department is among the best in the country.

It is truly an honor to be joining this great academic medical center.

Sincerely,

LISA KACHNIC, MD, FASTRO

CRR HISTORY TIMELINE

1916 Dr. Gioacchino Failla, a student of Marie Curie, established the **Radiological Research Laboratory (RRL)**, the predecessor of the Center for Radiological Research (CRR) at the New York's Memorial Hospital to improve the medical applications of radiation.

1919 Edith Quimby, the world's first woman medical physicist, joins the RRL and develops the "Quimby rules," a set of guidelines for where to place radium needles within a tumor for maximum therapeutic efficiency.

1922 The RRL constructs of the **first human phantom in the US** to determine the effects of filtration and distance on X-ray fields in the human body.

1930 Dr. Gioacchino Failla, and fellow Marie Curie student and colleague, Dr. William Duane, design and construct the **first radon generator in the US**, greatly reducing the cost and improving the efficiency of radiotherapy, which was based on radium at this time.

1942 The RRL moves to **Columbia University Irving Medical Center** to its current location in the Vanderbilt Clinic.

1950's Dr. Harold H. Rossi establishes the field of microdosimetry by providing the scientific underpinnings and equipment necessary to measure radiation. The microdosimetric detector, or "Rossi proportional counter", becomes vitally important for delivering accurate radiation therapy and providing radiation protection.

1960 Dr. Harold H. Rossi is named the new and second RRL director.

1967 In collaboration with the Brookhaven National Laboratory Medical Research Center, the RRL establishes the **Radiological Research Accelerator Facility (RARAF)**, a unique resource for radiobiology and radiological physics.

1972 RRL faculty member, Dr. Eric J. Hall publishes ***Radiobiology for the Radiologist***, the definitive radiation biology text for students of radiology and radiation oncology, now in its eighth edition.

1980 RARAF moves to Columbia University's **Nevis Laboratories**, located on the grounds of the 68-acre Nevis estate and mansion in Irvington, New York, established by one of Alexander Hamilton's sons.

1985 Dr. Eric J. Hall becomes the third director of the RRL, which is renamed the **Center for Radiological Research (CRR)**. CRR Faculty appointments are made through the parent Department of Radiation Oncology.

1990's RARAF designs and builds a **single-particle microbeam**, one of the few devices in the country capable of irradiating microscopic structures inside individual cells.

1996 Three CRR faculty, Drs. David J. Brenner, Tom K. Hei, and Howard B. Lieberman, are given joint appointments in the Department of Environmental Health Sciences at the Columbia University Mailman School of Public Health to address a growing need for **educating public health professionals in the safe use of radiation**.

1997 Publications of a series of papers in the *Proceedings of the National Academy of Sciences* on the biological effects of single alpha particles to specific cellular targets by Dr. Tom K. Hei and other members of the CRR help establish RARAF as the preeminent center for microbeam research.

1999 The CRR develops **hypofractionated radiotherapy**, which enables radiation to be given in larger doses and fewer treatments. Hypofractionated radiation becomes the universal standard treatment for prostate cancer - reducing radiotherapy visits from 40 to just 5.

2005 RARAF procures a new accelerator, the 5.5-megavolt Singletron, to support development of a microbeam that can focus protons and helium ions to within <1 micrometer.

2006 Dr. Howard B. Lieberman is elected **Fellow of the American Association for the Advancement of Science** for his breakthrough work in cloning yeast, mouse and human Rad9. The encoded protein, among other things, is known to check for DNA damage, has been found to repair DNA breaks as well as other types of damage, and is a key player in the regulation of radioresistance in cancer therapy.

2007 CRR faculty members, Drs. David J. Brenner and Eric J. Hall publish an influential paper in the *New England Journal of Medicine* on the **increased risk of cancer from CT scans, particularly in children**. Their research led to a national campaign to reduce CT exposure for children and resulted in the development of pediatric settings on CT scan machines.

2008 Dr. David J. Brenner is named the new and fourth CRR director.

2010 Drs. David J. Brenner and Sally A. Amundson expand the CRR's impact into the domain of national security by embarking on research to develop **practical radiation dose assessment devices** and techniques to be utilized in the event of large-scale radiological incidents.

2012 The **CRR Advisory Council** is established with Dr. P. Roy Vagelos serving as the Founding Chair.

2017 The CRR offers a **Master of Science degree in Radiological Sciences**, in conjunction with the Department of Environmental Health Sciences at the Columbia University Mailman School of Public Health.

2018 CRR faculty, in conjunction with the Department of Environmental Health Sciences at the Columbia University Mailman School of Public Health, design and establish an **annual Radiation Safety Officer training course** to fulfill Nuclear Regulatory Commission training requirements for individuals working in academia and industry.

CRR 2019 IMPACT

WE GET THE WORD OUT!

IN 2019, CRR
RESEARCHERS
PRESENTED

4

Keynote addresses at
international conferences

10

Invited talks and

5

Posters at national and
international conferences

12

Invited talks at Columbia
and other universities

THE CRR PROVIDES ADVISORS TO THE NATION AND THE WORLD



Sally A. Amundson and **Igor Shuryak** represented the CRR as members of the National Council on Radiation Protection and Measurements (NCRP). **Manuela Buonanno** became a member of NCRP Program Area Committee 7.



Members of the CRR served on advisory boards for the Environmental Protection Agency and the National Academies of Science.



6 CRR members served on advisory boards for institutions in Japan, China, and the European Union.

THE CRR PROVIDES LEADERSHIP, BOTH LOCALLY AND INTERNATIONALLY



WITHIN THE RADIATION RESEARCH SOCIETY (RRS)

Sally A. Amundson became Vice President Elect

Howard B. Lieberman chaired the History Committee

Manuela Buonanno chaired the Education and Website Committee



Tom K. Hei chaired the Radiation Research Foundation



Tom K. Hei was Chairman of the Commission for Life Sciences of the Committee on Space Research (COSPAR)

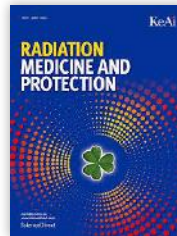


Manuela Buonanno served in the Columbia University Senate, and as a committee Vice Chair

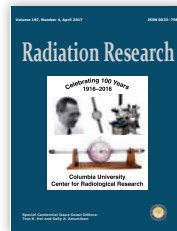
THE CRR SUPPORTS REPORTING OF ROBUST RESULTS



Tom K. Hei was Editor in Chief of *Life Sciences in Space Research*



Tom K. Hei was Co-Editor in Chief of *Radiation Medicine and Protection*



Howard B. Lieberman was a Senior Editor of *Radiation Research*

11 other CRR members served as Associate Editors and members of editorial boards

THE CRR SUPPORTS SELECTION OF THE STRONGEST RESEARCH PROPOSALS



Howard B. Lieberman chaired three NIH grant review panels



5 more CRR members served on NIH or NASA review panels

5 CRR members served on international or local review panels

CRR FACULTY



Sally A. Amundson, ScD

*Associate Professor
of Radiation Oncology*



Eric J. Hall, PhD

*Higgins Professor Emeritus
of Radiation Biophysics in
Radiation Oncology
Special Lecturer*



David J. Brenner, PhD, DSc

*Higgins Professor of Radiation
Biophysics (in Radiation
Oncology) and of Environmental
Health Science*

*Director, Center for Radiological
Research (CRR)*

*Director, Radiological Research
Accelerator Facility (RARAF)*



Tom K. Hei, PhD

*Professor of Radiation
Oncology and Environmental
Health Sciences*

*Associate Director, Center for
Radiological Research (CRR)*

*Vice-Chairman of Radiation
Oncology*



**Constantinos
G. Broustas, PhD**

*Assistant Professor of Radiation
Oncology (in the Center for
Radiological Research) at CUIMC*



Howard B. Lieberman, PhD

*Professor of Radiation Oncology
and Environmental Health
Sciences*



Guy Garty, PhD

*Associate Professor of Radiation
Oncology (in the Center for
Radiological Research) at CUIMC*

*Associate Director, Radiological
Research Accelerator Facility
(RARAF)*



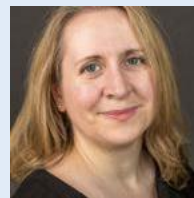
Igor Shuryak, MD, PhD

*Assistant Professor of Radiation
Oncology (in the Center for
Radiological Research) at CUIMC*



Shanaz A. Ghandhi, PhD

*Assistant Professor of Radiation
Oncology (in the Center for
Radiological Research) at CUIMC*



Helen C. Turner, PhD

*Associate Professor of Radiation
Oncology (in the Center for
Radiological Research) at CUIMC*



Peter W. Grabham, PhD

*Assistant Professor of Radiation
Oncology (in the Center for
Radiological Research) at CUIMC*



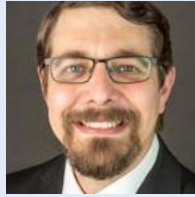
Jingsong Yuan, MD, PhD

*Assistant Professor of
Radiation Oncology*

CRR RESEARCH STAFF



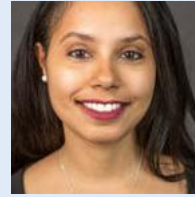
Manuela Buonanno, PhD
Associate Research Scientist



Andrew D. Harken, PhD
Associate Research Scientist



Brian Ponnaiya, PhD
Research Scientist



Maria Taveras, RN
Research Nurse

Kevin Hopkins, PhD
Senior Staff Associate

Ziyang Guo
Staff Associate

Cui Xia Kuan
Technical Assistant

Anthony LoMastro
Technician

Shad Morton
Senior Technician



Gloria M. Calaf, PhD
Adjunct Associate Research Scientist



Kevin Hopkins, MS
Senior Staff Associate



Gerhard Randers-Pehrson, PhD
Senior Research Scientist



Li Wang, PhD
Adjunct Associate Research Scientist

INSTRUMENT AND DESIGN SHOP

Robert Morton
Senior Instrument Maker

David Cuniberti
Instrument Maker

POSTDOCTORAL RESEARCH SCIENTIST

- Bezalel A. Bacon, PhD**
- Veljko Grilj, PhD**
- Seung-Yon Koh, PhD**
- Yuan-Cho Lee, PhD**
- Hazeem L. Okunola, PhD**
- Leah E. Nemzow, PhD**
- Ekaterina Royba, PhD**
- Hong-jian Wei, PhD**



Kunal R. Chaudhary, PhD
Associate Research Scientist



Gary W. Johnson
Senior Staff Associate, Instrument and Design Shop Director



Mikhail Repin, PhD
Associate Research Scientist



David Welch, PhD
Associate Research Scientist

ADMINISTRATION

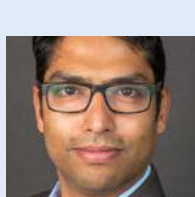
Margaret Zhu
Department Administrator

Margaret German
Administrative Assistant

Annerys Rodriguez
Junior Accountant



Charles R. Geard, PhD
Senior Biologist Emeritus



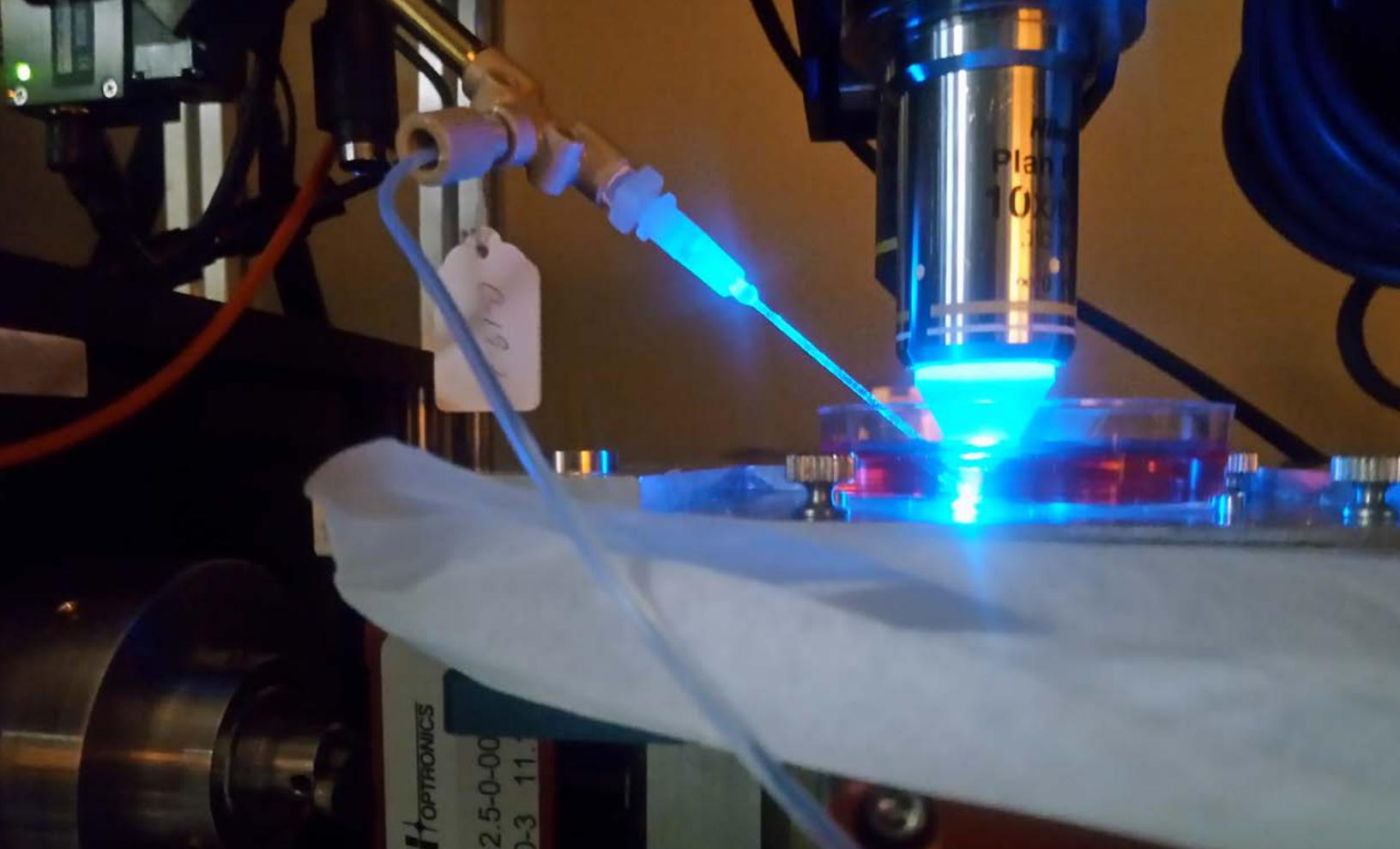
Sanjay Mukherjee, PhD
Associate Research Scientist



Enyuan Shang, PhD
Adjunct Associate Research Scientist



Xuefeng Wu, PhD
Associate Research Scientist



THE CENTER FOR RADIOLOGICAL RESEARCH 2019 RESEARCH SUMMARIES

The Center for Radiological Research (CRR) is a worldwide leader in unraveling the biological and molecular mechanisms underlying radiation effects in cells, tissues, organ systems, and living organisms. As such, CRR has a threefold research mission. Our scientists aim to advance knowledge about the effects of radiation exposure in living tissue; to provide the scientific basis and principles underlying the clinical use of radiation in the diagnosis and treatment of human disease; and to enhance national security by developing innovative rapid screening methods for assessing radiation exposure in large numbers of individuals in the event of an accidental or terrorist radiological emergency. The following sections include summaries of current groundbreaking research conducted by faculty members at CRR in the areas of nuclear disaster response, cancer, infectious disease, and space radiation.

NUCLEAR DISASTER RESPONSE



The recent Fukushima Daiichi nuclear disaster, as well as previous nuclear accidents in Chernobyl, Three Mile Island, and elsewhere have heightened concerns about the human health risks from accidental exposure to radiation. Despite research efforts, considerable uncertainty surrounds the long-term human health risks from prolonged and chronic low-level radiation exposure following such incidents. There is also growing concern over the anticipated need to rapidly identify those with higher radiation exposures in the dose range that could benefit from treatment in the aftermath of a dirty bomb attack or improvised nuclear device detonation. The goal of radiation biodosimetry is to accurately identify radiation dose and type, and to predict the extent of radiological injury in a large-scale radiation emergency of radiological injury in a large-scale radiation emergency. The following are summaries of current investigations at CRR focused on nuclear disaster response.

DEVELOPMENT OF AN INTEGRATED FINGERSTICK BLOOD SELF-COLLECTION DEVICE

CRR Lead Investigator:

Sally A. Amundson, ScD,
Associate Professor of Radiation Oncology

Project Principal Investigator:

Frederic Zenhausern, PhD, MBA,
*Professor of Basic Medical Sciences,
Director of University of Arizona Center
for Applied NanoBioscience and Medicine*

Collaborators (at Columbia):

Drs. Sanjay Mukherjee, Mikhail Repin

David J. Brenner Collaborators (at the University of Arizona Center for Applied NanoBioscience and Medicine):

Drs. Jian Gu, Alan Norquist, Carla Brooks,
Jerome Lacombe, and Jianing Yang

Within the Center for High Throughput
Minimally Invasive Radiation Biodosimetry,

the teams of Dr. Sally A. Amundson and Dr. Frederic Zenhausern have joined forces to address one of the critical potential bottlenecks in large-scale biodosimetry—blood sample collection. They have developed an integrated fingerstick blood collector that allows the public to self-collect blood samples suitable for radiation biodosimetry testing. The necessary components for running tests based on gene expression or cytogenetics are sealed within the collector, ensuring stable samples can be collected without previous training or experience. Dr. Amundson and her collaborators showed that these blood samples gave the same results as blood collected from the vein by trained phlebotomists. Dr. Mikhail Repin leads efforts to show the same for cytogenetic endpoints. This collector could enable rapid sample collection for radiation countermeasures following a large-scale nuclear event. It could also be adapted to many other applications, such as checking viral titers during pandemic outbreaks, or sample collection for screening tests in remote or underserved areas.

GENE EXPRESSION FOR RADIATION BIODOSIMETRY

Principal Investigator:

Sally A. Amundson, ScD,
Associate Professor of Radiation Oncology

Collaborators:

Drs. Shanaz A. Ghandhi, Sanjay Mukherjee, and Shad Morton

Dr. Sally Amundson and her collaborators continue to develop gene expression signatures that help detect individuals who have been exposed to potentially dangerous levels of radiation. In a collaboration with Drs. Albert Fornace and Evagelia Laiakis, they looked at how chronic inflammatory conditions might change the gene expression response to radiation. With Drs. Constantinos C. Broustas, Veljko Grilj, Andrew D. Harken and Guy Garty, Dr. Amundson and her colleagues have

continued their examination of the impact on gene expression when neutrons make up varying percentages of the total dose. They also collaborated with Drs. David J. Brenner and Igor Shuryak, to develop a quantitative dose reconstruction approach from the large amount of data the team has previously collected. Their characterization of the mouse as a model for radiation response resulted in the publication of a large-scale analysis of dose-dependent gene expression patterns during the first week after exposure, in a joint effort with Dr. Norman J. Kleiman and former lab member Dr. Sunirmal Paul.

THE IMPACT OF AGING ON RADIATION BIODOSIMETRY

Principal Investigator:

Constantinos G. Broustas, PhD,
Assistant Professor of Radiation Oncology (in the Center for Radiological Research) at CUIMC

Gene expression profiling represents a promising method of biodosimetry. However, for a gene expression signature to be useful, it should be applicable across diverse populations irrespective of age, gender, or environmental and genetic backgrounds.

Aging is characterized by random and widespread unrepaired damage to DNA, as well as gene expression changes that may compromise the predictive value of radiation biodosimetry. Dr. Broustas's studies are designed to investigate the impact of aging on the response to radiation, by using total body irradiation combined with transcriptomics analysis of whole blood cells from young and old mice, as well as *ex vivo irradiated human blood*.

Dr. Broustas and his collaborators have demonstrated that aging promotes a large-scale rewiring of transcriptional networks that alters the response to radiation exposure. Therefore, age should be considered a determinant for the development of gene signatures applicable to radiation biodosimetry.

The results from this study will help to define a consensus gene signature that is valid across various age groups, helping to improve overall survival of all individuals exposed to ionizing radiation. Furthermore, a greater understanding of the stress response signaling during aging may provide new insight in age-related diseases.

AUTOMATING BIODOSIMETRIC ASSAYS USING COMMERCIAL ROBOTIC PLATFORMS

Principal Investigator:

Guy Garty, PhD,
*Associate Professor of Radiation Oncology
(in the Center for Radiological Research)
at CUIMC*

The dicentric chromosome assay (DCA) is recognized as the gold standard in radiation biodosimetry by the International Atomic Energy Agency (IAEA), the International Organization for Standardization (ISO) and the US Food and Drug Administration (FDA). DCA is based on identifying misrepaired, irradiated, chromosomes, containing two centromeres, rather than the normal one. However, the conventional DCA is labor intensive and can only realistically be used for small incidents (10s to 100s of individuals).

Leveraging his previous work in automating biodosimetry assays using both custom and off the shelf robotics, Dr. Garty and his team implemented the DCA on a commercial High Throughput Screening platform. These systems are widely used to perform chemical, genetic or pharmacological tests in universities and in the pharmaceutical industry. Implementing biodosimetry assays on these platforms will enable their wide deployment, significantly increasing the capacity for running these assays in an emergency.

In parallel, Dr. Garty and his colleagues have continued their work on improving their automated micronucleus assay. They have developed an accelerated version as well as a

variant that does not require a centrifuge and can be performed on a wider range of robotic platforms. The automated assays they have developed based on a fingerstick of blood processed in batches of 96 in a multiwell plate, and provide results similar to the classical assay at significantly higher throughput and without human involvement.

TRANSCRIPTOMIC BIODOSIMETRY IN MODELS OF COMPLEX RADIATION EXPOSURES

Principal Investigator:

Shanaz A. Ghandhi, PhD,
*Assistant Professor of Radiation Oncology
(in the Center for Radiological Research)*

Dr. Ghandi is conducting several studies in the area of nuclear disaster response, including the following:

Non-human primate transcriptomic response to radiation: This is an ongoing study on gene expression response of NHPs to radiation. Dr. Ghandhi and her collaborators identified and validated novel biomarkers for radiation and survival in this *in vivo* model system.

Radiation gene expression in complex scenarios: Dr. Ghandhi developed a gene expression based methodology for reconstructing dose and dose-rate that an individual may be exposed to in a radiological event. She studied the effects of dose-rate and internal emitters on blood gene expression to develop a bio-dosimeter and to study the mechanistic underpinnings of the response to radiation.

Humanized mouse and radiation response: Dr. Ghandhi and her team validated a novel *in vivo* model of radiation response in hematopoietically humanized mice. New models to study radiation response are critical for overcoming the limitations of working with human cells in an *in vivo* context. This ongoing study aims to determine differences between mouse and human gene expression response to stress.

NEW RADIATION BIODOSIMETRY APPROACHES FOR QUANTITATIVE DOSE RECONSTRUCTION

Principal Investigator:

Igor Shuryak, MD, PhD,
Assistant Professor of Radiation Oncology (in the Center for Radiological Research) at CUIMC

Collaborators:

Drs. Shanaz A. Gandhi, Helen C. Turner,
Sally A. Amundson and David J. Brenner

Dr. Shuryak and his collaborators recently performed a proof-of-principle study applying new methods to select radiation-responsive genes to generate quantitative, rather than categorical, radiation dose reconstructions based on a blood sample. They used a new normalization method to reduce effects of variability of signal intensity in unirradiated samples across studies; developed a quantitative dose-reconstruction method; and combined these to determine a gene set as a dose reconstructor. Their approach was trained using two data sets and tested on two independent ones. This approach can accurately reconstruct dose with minimal error, and outperforms those published elsewhere.

DEVELOPMENT OF THE FAST-DOSE ASSAY SYSTEM FOR HIGH-THROUGHPUT BIODOSIMETRY AND POPULATION TRIAGE

Principal Investigator:

Helen C. Turner, PhD,
Associate Professor of Radiation Oncology (in the Center for Radiological Research) at CUIMC

Most of Dr. Turner's research is focused on developing novel high-throughput radiation biodosimetry platforms for the automation of protein-based assays. Recently, Dr. Turner and her colleagues developed a biomarker-based assay platform named FAST-DOSE (Fluorescent Automated Screening Tool for Dosimetry) to measure radiation-

responsive proteins in human peripheral blood samples. The biomarker panel was developed from proteomic profiling of irradiated blood lymphocytes *in vivo* from hematopoietically humanized mice. The FAST-DOSE biomarker-based platform combines a commercial imaging flow cytometry system (ImageStream®X) and associated Image Data Exploration and Analysis Software to rapidly quantify changes in intracellular protein biomarkers using fluorescent imagery and algorithms for estimation of absorbed dose. Her objective is to optimize and validate the FAST-DOSE assay system and biomarker protein panel to reconstruct dose in human blood leukocytes after ionizing irradiation. In the past year, Dr. Turner and her team started to acquire performance data for the individual biomarkers and evaluate their sensitivity and dose-response in human blood leukocytes up to three days after radiation exposure. In collaboration with Dr. Igor Shuryak, she will develop mathematical models to select the best FAST-DOSE biomarkers and to estimate radiation dose based on measured biomarker levels, demographic and confounding factors.

MEASUREMENT OF THE DNA RESPONSE IN BLOOD LEUKOCYTES IN VIVO AFTER VARIABLE, LOW-DOSE RATE CS-137 EXPOSURE

Principal Investigator:

Helen C. Turner, PhD,
Associate Professor of Radiation Oncology (in the Center for Radiological Research) at CUIMC

Cesium-137 (Cs-137), a fission product of uranium and plutonium, is a radionuclide of concern following the detonation of an improvised nuclear device or a nuclear reactor accident. In the past year, Dr. Turner and her colleagues collaborated with Dr. Waylon Weber and his team at Lovelace Biomedical (Albuquerque, NM), to investigate γ -H2AX repair kinetics in mouse blood following a single injection of Cs-137 radionuclide. A key finding of this work was that measurements of

γ -H2AX, a biomarker for DNA double strand breaks identified persistent DNA damage in the mouse peripheral blood leukocytes *in vivo* that allowed Dr. Turner to accurately predict injected Cs-137 activity 2-5 days after initial exposure. This is in contrast with acute exposures where the γ -H2AX signal is typically undetectable after ~24-48 hours depending on dose. Recently, in collaboration with Dr. Guy Garty, Dr. Turner extended this work using the novel Variable Dose-rate External Cs-137 irradiator (VADER) which is designed to provide arbitrarily varying and constant

low dose rate irradiations in the range 0.1-1.2 Gy/day, while circumventing the complexities of dealing with radioactively contaminated biomaterials. Measurement of γ -H2AX levels after progressively decreasing low-dose rate external exposures over seven days with accumulated doses ranging from 0.49 Gy (day 1) to 2.68 Gy (day 7) showed that the γ -H2AX endpoint was able to provide a good discrimination of accumulated dose < 2 Gy and \geq 2 Gy, highlighting the potential of γ -H2AX as a dosimetry biomarker in a protracted, low-dose rate exposure scenario.



ADVANCING CANCER TREATMENT

Research conducted at the CRR aims to continuously improve radiation therapy techniques in order to eliminate cancer while minimizing unwanted side effects. The CRR's groundbreaking contributions to cancer treatment include increasing the accuracy and precision of radiotherapy for patients by developing the measuring equipment and dosage guidelines used by radiotherapists worldwide. For prostate cancer, our researchers are focused on originating treatment methods

that enable radiation to be given in larger and fewer doses—reducing radiotherapy visits for prostate cancer from 40 to just five. In pancreatic and other hard-to-treat metastatic cancers, our faculty members are investigating how carbon ion radiation and other heavy charged particles can affect long-range immunological response and improve treatment. Studies are also underway to identify novel anti-cancer targets as part of a precision medicine approach to develop new treatment

strategies for patients with prostate cancer. In breast cancer, we are exploring improved treatments, including non-invasive alternatives to mastectomy for patients with BRCA1/2 gene mutations, as well as methods to reduce the risk of a second breast cancer.

This section highlights innovative basic and translational studies initiated by CRR faculty members focused on improving treatment for different forms of cancer including head and neck cancer, glioblastoma, prostate cancer and breast cancer. It also showcases cutting-edge technologies and tools developed by CRR faculty and housed at RARAF that support our novel cancer research efforts.

INTEGRATED SINGLE CELL TRACKING AND GENE EXPRESSION MEASUREMENTS IN RARE CELLS

Principal Investigator:

Sally A. Amundson, ScD,
Associate Professor of Radiation Oncology

Collaborators:

Drs. Junyi Shang, Timothy Olsen, Qiao Lin, Brian Ponnaiya, Manuela Buonanno, and David Welch

Dr. Amundson and her collaborators at the CRR and in Dr. Lin's lab in the Department of Mechanical Engineering have developed an integrated microfluidic device for coupling the precise irradiation of individual cells with quantitative gene expression measurements on a cell-by-cell basis. For the first time, this allows the tracking of individual irradiated or bystander cells, so that the gene expression measurements can be identified with a specific cell. Dr. Amundson and her colleagues used this method to measure genes in two different signaling pathways, TP53 and NFκB, and demonstrated that within a cell, the levels of genes in the same pathway were highly correlated, both before and after radiation exposure. In contrast, there was no correlation between the expression levels of genes in different pathways in un-irradiated cells.

However, following radiation exposure, there was a slight inverse correlation between genes in the different pathways, suggesting that there is a balance of activation between the TP53 and NFκB pathways and that the two pathways compensate for each other to some extent within an individual cell.

This unique cell-handling and tracking approach will enable the study of rare cells in populations in order to improve our understanding of mechanisms of differentiation in tissue function and development as well as for disease diagnostics and cancer treatment.

A NEW PROTON FLASH IRRADIATOR AT RARAF: INITIAL BIOLOGICAL STUDIES IN NORMAL CELLS

Principal Investigator:

Guy Garty, PhD,
Associate Professor of Radiation Oncology (in the Center for Radiological Research) at CUIMC

Collaborators:

Drs. Manuela Buonanno, Veljko Grilj, and David J. Brenner

Radiotherapy outcomes are limited by the toxicity to the healthy tissues surrounding the irradiated tumor. Promising pre-clinical studies have shown that irradiations with electrons or photons delivered at so called FLASH dose rates (i.e. > 40 Gy/s) dramatically reduced adverse side effects in the normal tissues while being equally efficient for tumor control as irradiations at conventional dose rates (3-5 cGy/s). In the case of protons however, FLASH effects have not been investigated partially because of the limited availability of facilities that can achieve such high dose rates.

Dr. Guy Garty and his collaborators assembled a novel experimental platform for proton FLASH irradiations that is capable of delivering dose rates of up to 1000 Gy/s to a circular area of 10 mm diameter. They developed a straightforward film dosimetry protocol to calibrate the system and assure accurate dose delivery regardless of the instantaneous dose

rate. Besides the versatile custom designed holders for irradiation of cells, 3D tissues and mice, they manufactured a PDMS-based microfluidic flow-through device that allows for irradiations of biological samples in suspension. In summary, the proton dose rate had little impact on acute effects in normal cells as well as several cancer cells under normoxic conditions; however, the dose rate of protons significantly influenced the expression of long-term biological responses *in vitro*. Compared to conventional dose rates, protons delivered at FLASH dose rates mitigated such delayed detrimental effects.

IN-VIVO IMMUNOGENIC EFFECTS OF HIGH LET CHARGED PARTICLE RADIATION: PROOF OF PRINCIPLE

Principal Investigator:

David J. Brenner, PhD, DSc,
Higgins Professor of Radiation Biophysics (in Radiation Oncology) and of Environmental Health Sciences

Collaborators (at Columbia):

Drs. Brian Ponnaiya, Manuela Buonanno, Veljko Grilj, and Gary W. Johnson

Collaborators (at the Department of Radiation Oncology, Weill Cornell Medical College):

Drs. John Ng, Francesca Khani, Ayush Rana, Takahiro Yamazaki, Lorenzo Galluzzi, and Silvia C. Formenti

For an equivalent dose, high linear energy transfer (LET) particle irradiation offers many potential therapeutic advantages over X-rays, including: enhanced direct tumor cell kill; induction of more complex DNA damage, which is more difficult to repair; and sparing more immune cells such as active effector and memory T cells that are necessary to mount an effective immune response (due to their dose distribution).

One of the most promising strategies against cancer is the combination of local radiation therapies with immunotherapy as a way

to convert the individual tumor to an *in-situ* vaccine. It is speculated that radiation induces in tumors a form of cell death, called immunogenic cell death, which leads to the release of immunostimulatory signals.

Indication that high LET particles may enhance the immune response compared to photon-based radiation therapy, comes from the substantial increase in the survival of patients with locally advanced pancreatic cancer following carbon ion therapy. In the field of particle therapy, helium ion beams could offer a lower-cost alternative for radiotherapy treatments, due to their unique physical and biological properties intermediate between protons and carbon ions.

Dr. Brenner and his collaborators investigated the immunogenic effects of helium ions compared to X-rays, using an established in-vivo breast cancer model. Ongoing experiments aim to investigate the immunogenic potential of high LET radiation using a model of pancreatic cancer, which is one of the hardest tumors to treat. The study so far has won three travel awards for poster presentation from the Radiation Research Society and the American Society for Therapeutic Radiology and Oncology (ASTRO).

RADIATION INDUCED NON-TARGETED RESPONSE

Principal Investigator:

Tom K. Hei, PhD,
Professor of Radiation Oncology, Professor of Environmental Health Sciences

Collaborators (at Columbia):

Drs. Jason Yuan, Guy Garty, and Charles Drake

Collaborator (at Rutgers University at New Jersey Cancer Center):

Dr. Edouard Azzam

Ionizing radiation can both cure as well as induce human cancer, including those derived as a result of radiotherapy. There is evidence that approximately five to 18 percent

of pediatric radiotherapy patients develop radiation-induced secondary tumors and many of these tumors arise at a distance far away from the treatment field. While there is evidence that radiation delivered to the abdomen of genetically susceptible mice resulted in the development of brain tumors, the underlying mechanisms and health relevance to humans are unknown.

The overall goal of Dr. Hei's project is to elucidate the how and why of radiation induced secondary tumors using well defined *in vitro* and *in vivo* models to examine the role of inflammatory events characterized by cyclooxygenase-2 (COX2) signaling and immune modulation. To simulate a clinical radiotherapy scenario, an orthotopic breast cancer model will be used in conjunction with a CT-guided small animal irradiator to define non-targeted response in out-of-field tissues. A better understanding of the mechanism and clinical relevance of the non-targeted/abscopal response is central to an accurate assessment of cancer risk induced by ionizing radiation.



TECHNOLOGICAL DEVELOPMENTS: CANCER AND HEAVY IONS AT RARAF

Principal Investigator:

David J. Brenner, PhD, DSc,
Higgins Professor of Radiation Biophysics (in Radiation Oncology) and of Environmental Health Sciences

Collaborators:

Drs. Andrew D. Harken, Guy Garty,
Christian Siebenwirth, and Veljko Grilj

Treating cancer with the use of particles instead of x-rays for radiation has taken off in recent years. The use of proton therapy in the U.S. has become commonplace with many proton therapy centers coming online across the country. While protons have been therapeutically effective, there is the question of using 'heavier' particles such as carbon ions. Several centers outside the U.S. are testing heavier ions in cancer therapy. While therapeutically effective, the difference between proton and heavier ion therapy is not mechanistically known at the cellular level.

RARAF is ideally suited for studying radiation effects at the cellular level, however, the configuration of the RARAF Singletron accelerator did not previously allow for the generation of heavier ions. This year Dr. Brenner and his colleagues advanced the development of a heavy ion source in the RARAF accelerator that will have the capability to produce these heavy ions. They have worked with the DREEBIT Electron and Ion Beam Technologies, GMBH, for the development of one of their electron beam ion trap (EBIT) particle sources for operations within our accelerator. This required modification from their standard designs for power consumption, heat dissipation, ion beam extraction, and overall operational parameters. Dr. Brenner and his collaborators installed the EBIT source in the RARAF accelerator and started testing the heavy ion beams in the RARAF experimental stations. They anticipate offering the heavy ion beams to RARAF users in 2020.

FLEXIBLE TOOLS FOR PRE-CLINICAL STUDIES TO ANSWER KEY QUESTIONS UNDERLYING HEAVY-ION RADIOTHERAPY

Principal Investigator:

David J. Brenner, PhD, DSc,
Higgins Professor of Radiation Biophysics (in Radiation Oncology) and of Environmental Health Sciences

Collaborators at the CRR:

Drs. Sally A. Amundson, Andrew D. Harken, Guy Garty, Peter Grabham, Brian Ponniaya

There is currently strong interest in the introduction of Heavy-ion radiation therapy (HIRT) to the U.S., largely-based on the experience of carbon-ion radiotherapy in Japan and Germany, where encouraging survival rates have been reported for a number of hard-to-treat cancers such as pancreas, rectum, and sarcoma. For example, two-year survival of >60 percent has been reported after carbon-ion therapy for locally-advanced pancreatic cancer, which is remarkably encouraging at a post-treatment time when survival is dominated by distant metastases. Thus, there has been much discussion that, as well as producing local effects to the tumor, HIRT may also include long-range systemic anti-cancer effects. However, the underlying mechanisms for such high-LET-induced long-range systemic effects are not understood. Dr. Brenner's team will study cellular and 3D tissue models for the effect of heavy ions on cancer.

STRATEGIES TO IMPROVE RADIOTHERAPY OF PROSTATE CANCER

Principal Investigator:

Constantinos C. Broustas, PhD,
Assistant Professor of Radiation Oncology (in the Center for Radiological Research) at CUIMC

Radiotherapy is a common therapeutic modality for treating human epithelial tumors including those of prostate origin. However, tumor resistance to ionizing radiation caused

by a number of pro-survival mechanisms, including elevated DNA repair capacity, remains a major obstacle. Furthermore, signal transduction pathways, such as the PI3K/AKT and MAPK pathways, which are often aberrantly activated in tumors, can mediate radio-resistance. Thus, inhibiting these pathways with specific inhibitors is a promising strategy for increasing tumors' radio-sensitivity.

Dr. Broustas is conducting research that focuses on the cross-talk between oncogenic signal transduction pathways and DNA damage response and repair in prostate cancer and therapeutic resistance. He and his team have shown that mitogen/extracellular signal-regulated kinase kinase-5 (MEK5), a member of the MAP kinase family, is a major determinant for mediating radiation resistance in prostate cancer, using cancer cell lines and animal models. MEK5 downregulation results in the reduction of tumor DNA repair capacity in response to genotoxic assault and the sensitization of tumor cells. Importantly, combination of radiotherapy with MEK5 ablation leads to substantial tumor growth inhibition in mice. Ultimately, Dr. Broustas aims to develop a small molecule inhibitor of MEK5 that in combination with radiation will sensitize tumor cells and maximize the curative potential of radiation therapy for patients with localized prostate cancer.

PROSTATE CANCER

Principal Investigator:

Howard B. Lieberman, PhD,
Professor of Radiation Oncology and Professor of Environmental Health Sciences

Collaborators:

Drs. Constantinos G. Broustas, Israel Deutsch, Richard A. Friedman, Renu Virk, and Sven Wenske

Effective treatment of metastatic prostate cancer patients remains a major medical challenge. The American Cancer Society

estimated there were 174,650 new cases of prostate cancer diagnosed in the U.S. in 2019 alone, and a staggering 31,620 of those individuals will die from it, largely due to metastatic disease. Current drugs help men with the malignant disease live longer, on average, but rarely provide a cure. The goal of this project is to evaluate a unique pathway, involving aberrant overproduction of the RAD9 protein that drives prostate cancer. Dr. Lieberman's investigations are focused on better understanding the role of RAD9 and related signaling proteins in the disease, and using the information gained to develop novel, improved diagnostics and urgently needed precision anti-cancer targets for men with malignant prostate cancer.

CANNABIS, RADIATION AND GLIOBLASTOMA

Principal Investigator:

Tom K. Hei, PhD,
Professor of Radiation Oncology,
Professor of Environmental Health Sciences

Collaborator:

Dr. Fred Wu

Glioblastoma (GBM) is the most common primary brain cancer affecting more than 12,000 new patients in the U.S. each year. Surgery followed by external beam radiation and chemotherapy (Temozolomide) is the standard of care for GBM. However, prognosis for the disease remains poor with a median survival rate of 12-15 months after initial diagnosis. In addition, radiation treatment to the brain is associated with loss of cognitive function and memory. There is an urgent need for newer and more effective means of therapy.

Due to the changing policies in government regulation of medical marijuana, more cancer patients, including glioma patients, are offered cannabinoids (CBs) as part of their treatment, primarily for its palliative effects to reduce nausea, emesis and pain associated with

chemoradiation. There is evidence that CBs can directly affect glioma cells, as well as non-neoplastic cells in the surrounding brain tissue, and may even have therapeutic functions via effects on glioma cell proliferation, apoptosis and autophagy.

The overall goal of Dr. Hei's project is to systematically examine the positive and negative effects of two main cannabinoids, THC and CBD, to the brain parenchyma and GBM within the context of radiotherapy. Due to this growing patient use of cannabis with intracranial radiation, there is an urgent public health need to investigate both the potential positive and negative effects of its use. Findings from this study will be robust because either positive or negative outcomes will help bring clarity to the heavily debated usage of medical cannabis in patients with intracranial tumors.

RADIOTHERAPY OPTIMIZATION TO IMPROVE TUMOR CONTROL AND DECREASE LATE EFFECTS FOR HEAD AND NECK CANCERS

Principal Investigator:

Igor Shuryak, MD, PhD,
Assistant Professor of Radiation Oncology (in the Center for Radiological Research) at CUIMC

Collaborators:

Drs. Eric J. Hall and David J. Brenner

Head-and-neck cancers (HNC) occur in approximately 53,000 people per year in the U.S., and kill 11,000 individuals each year. Treatment of fast-growing HPV-negative HNC remains challenging due to frequent local control failures and/or tumor recurrences. New methods that improve the radiotherapeutic effectiveness balance between tumor control probability (TCP) and late normal-tissue complication probability (LNTCP), compared with standard fractionation, are needed. Dr. Shuryak and his collaborators address this challenge by using systematic radiobiological optimization, where they track

the development after each treatment fraction of both tumor control and late sequelae. They developed an improved model of accelerated repopulation, calibrated with extensive HNC clinical trials data, and used it to identify optimally effective treatment regimens that increase TCP and decrease LNTCP. For comparison, they also used standard repopulation models.

Dr. Shuryak's results show that an optimized hypofractionated schedule of 18×3.0 Gy is predicted to substantially increase TCP, while decreasing high-grade LNTCP, as compared with a standard 35×2.0 Gy protocol. In addition, the treatment time is reduced from 47 to 24 days. Twice-daily treatments of 1.8 Gy/fraction provide even better outcomes. These results suggest that hypofractionation or accelerated hyperfractionation both overcome tumor repopulation, and can be optimized towards the end of treatment when repopulation causes the TCP to increase only very slowly while LNTCP is increasing rapidly. Specifically, 3.0 Gy/fraction hypofractionation is predicted to be considerably more effective for HNC tumor control and for reduction of late effects, than standard 2.0 Gy fractionation.

PROPHYLACTIC MAMMARY IRRADIATION (PMI)

Principal Investigator:

Igor Shuryak, MD, PhD,
Assistant Professor of Radiation Oncology (in the Center for Radiological Research) at CUIMC

Collaborator:

Dr. David J. Brenner

Long-term breast cancer survivors have a highly elevated risk of contralateral second breast cancer due to pre-malignant cells in the contralateral breast, which can eventually develop into tumors. There is a need for preventative approaches beyond prophylactic contralateral mastectomy, tamoxifen and aromatase inhibitors to reduce these



disturbingly high long-term risks in breast cancer survivors and in women with genetic breast cancer predisposition. Dr. Shuryak proposed a novel concept that an appropriate Prophylactic Mammary Irradiation (PMI) dose of x-rays to the contralateral breast, delivered at the same time as radiotherapy to the cancer-bearing breast, but using a lower dose, can kill pre-malignant cells, strongly reducing the contralateral breast cancer risk. He and his team tested this hypothesis in a proof of principle study using a transgenic mouse model of aggressive breast cancer (Shuryak et al. PLoS One. 2013;8:e85795). These mice develop multiple mammary tumors at an early age. An optimal PMI regimen resulted in two to three-fold reduction in mammary tumorigenesis. Subsequently, a Phase II clinical trial of PMI in humans was conducted in Israel, with very encouraging results: five-fold reduction of contralateral breast cancer risk was observed (Evron et al. Ann Oncol. 2019 Mar 1;30(3):412-417). Grant applications are in process for a more detailed investigation and optimization of PMI regimens in more realistic mouse models of mammary cancer than those used in the proof of principle study, in terms of later age of onset and lower tumor multiplicity.

ENDOTHELIAL NOTCH REGULATION OF TUMOR IMMUNE RESPONSE TO HIGH-DOSE RADIATION THERAPY

Principal Investigator:

Eileen Connolly, MD, PhD

Assistant Professor,

Department of Radiation Oncology

Collaborators:

Drs. Peter Grabham, David Welch, Darrell Yamashiro, Kevin Kalinsky, Rami Vanguri, and Hanina Hibshoosh

Immunotherapy (IO) has revolutionized cancer therapy. Nevertheless, only a minority of patients respond to single drug therapy. High-dose radiation therapy (HDRT) has a profound immuno-stimulatory effect on tumors and

is being evaluated as an adjuvant. However HDRT also induces an immunosuppressive response by attracting immunosuppressive cells like regulatory T-cell (Treg), and tissue-associated macrophages (TAM). It is not completely understood how HDRT modulates the immune landscape. Endothelial cells (ECs) are a major component of tumor microenvironment (TME) and influence physiological and pathological conditions. Dr. Eileen Connolly's lab has established that HDRT increases Notch1 signaling in tumor ECs, which induces endothelial-to-mesenchymal-transition (EndMT). Preliminary data further demonstrates that HDRT-induced EndMT is associated with increased M2-type macrophages and Treg cells. They hypothesize that HDRT-induced EndMT, regulated by EC Notch1 signaling, enhances immunosuppressive immune response by increasing these cell populations. Dr. Connolly's goal is to determine how endothelial Notch1-induced EndMT regulates the immunosuppressive immune cell populations following HDRT, and to demonstrate that adding Notch targeted agents in combination with HDRT and IO improves treatment efficacy.

In addition to studying TME in animal models, Dr. Connolly is interested in understanding risk factors for regional recurrence in breast cancer patients following neoadjuvant chemotherapy (NAC). She has built a comprehensive database of all breast cancer patients treated with NAC at CUIMC from 2002 - 2019, from which her lab has been able to look at patterns of failure and predictors of survival. Additionally, they have pulled patient samples pre and post NAC to evaluate the TME for immune biomarkers predicting response to therapy and risk for recurrence in breast cancer. Finally, they are working with Eisai to determine if baseline characterization of the TME by qmIF can predict response of patients with metastatic TNBC treated on the ENHANCE 1 trial with Eribulin and Pembrolizumab comparing responders to non-responders.

FOCUSED ULTRASOUND AND RADIATION FOR GLIOMAS

Principal Investigator:

Cheng-Chia “Fred” Wu, MD, PhD
Assistant Professor,
Department of Radiation Oncology

Collaborators:

Drs. Tom K. Hei, David Welch, Elisa Konofagou, Stergios Zacharoulis, Alexis Maddocks, Neil Feldstein, and Jia Guo

Gliomas are deadly brain tumors that are challenging to treat. The tumor is heterogeneous: the solid component is surgically removed and the remaining microscopic disease is treated with chemotherapy and radiation. The microscopic disease is infiltrative and often extends to regions of the brain where the blood brain barrier remains relatively intact. This makes it difficult for systemic therapies to reach the tumor cells in the brain.

Focused Ultrasound (FUS), when combined with microbubbles, delivers non-invasive soundwaves (non-ionizing radiation) to selectively open the blood brain barrier (BBB). Dr. Fred Wu’s laboratory is interested in exploring the combination of ionizing radiation with FUS-targeted BBB opening for new drug therapies and immunotherapy. Working with the Center for Radiological Research (CRR), they have established small animal models for magnetic resonance imaging (MRI) guided radiotherapy to the brain. In collaboration with Dr. David Welch, they have validated a murine quality assurance methodology using an anthropomorphic phantom system for brain radiation planning. They are also collaborating with the Department of Biomedical Engineering, the Zuckerman Institute, Pediatric Neuro-Oncology, Pediatric Neurosurgery, and Pediatric Radiology to translate this technology to clinic application.

Dr. Wu’s laboratory was recently funded for a Phase 0 clinical trial to test the feasibility of FUS-mediated blood brain barrier opening

in pediatric patients with brain tumors. Dr. Wu’s goal is to revolutionize the treatment paradigm for brain tumors through advanced translational research, bridging the gap between basic science and clinical medicine.

THERAPY RESISTANCE PATHWAYS IN TUMORS

Principal Investigator:

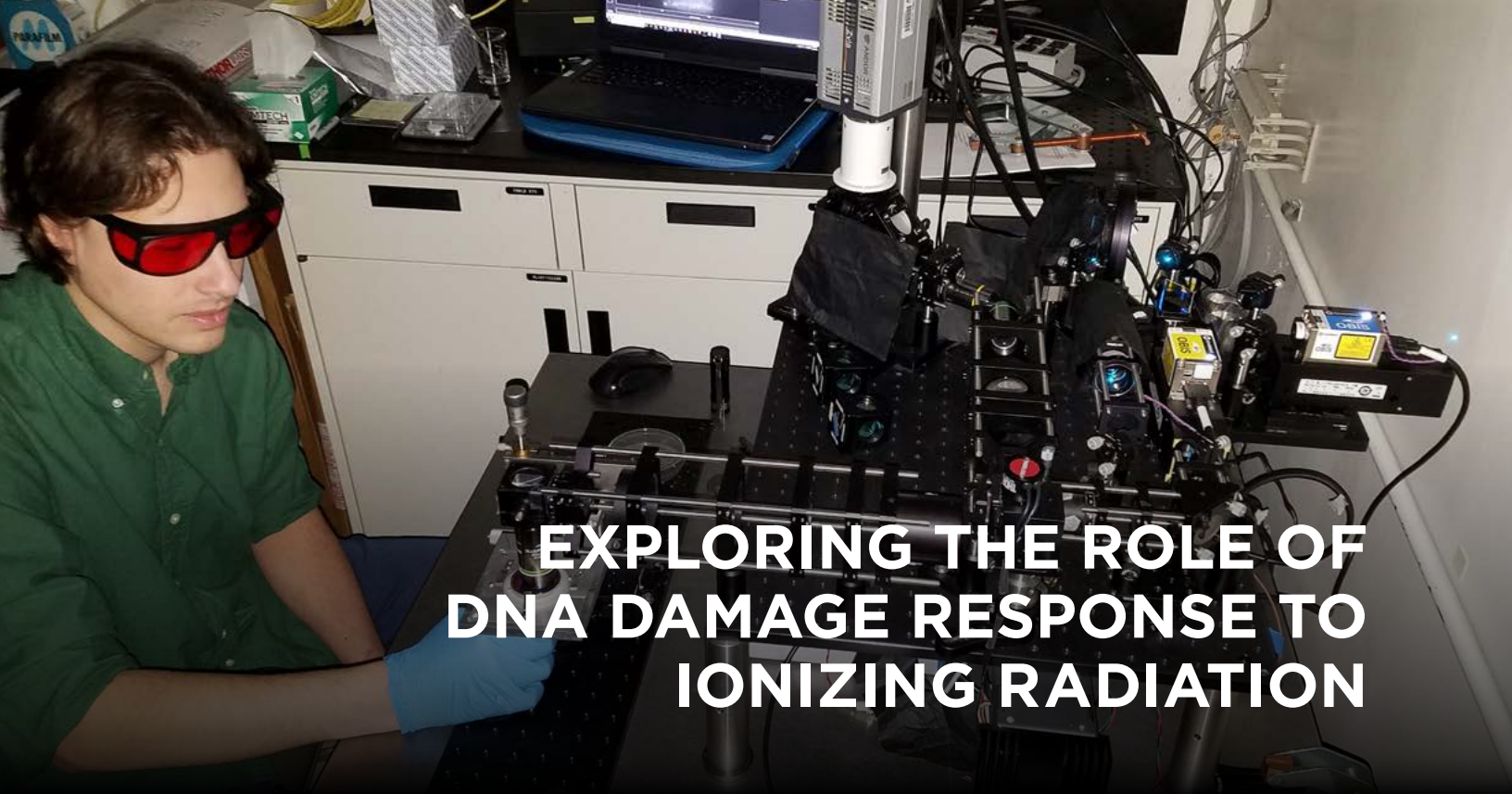
Simon K. Cheng, MD, PhD
Assistant Professor,
Department of Radiation Oncology

Collaborators:

Drs. Tom K. Hei, Jingsong Yuan, Manuela Buonanno, Guy Garty, Brent Stockwell, Peter Canoll, Jeffrey Bruce, Naiyer Rizvi, Catherine Shu, and Brian Henick

Dr. Simon Cheng’s research interest is focused on enhancing the effectiveness of radiation therapy and immunotherapy in lung and brain tumors using innovative experimental platforms. His research approach is divided into two programs: 1) a translational laboratory group dedicated to uncovering the biological mechanisms of radiation and immunotherapy resistance in tumors; and 2) a data science group examining the interaction of patient factors, such as seemingly unrelated incidental medications use and community flu incidence, on treatment response and patient survival.

Dr. Cheng’s main project within the CRR is on ferroptosis, which is an emerging mechanism of cell death that is tightly integrated with nutrient availability and cellular metabolism. His lab has recently reported that gamma radiation induces ferroptosis, and ferroptosis-inducers are radiosensitizers in cancer, including lung cancers, sarcomas, and glioblastoma. He is currently exploring the effects of the advanced delivery of high LET radiation and ultra-high dose rate FLASH radiation on ferroptosis. These studies will pave the way for the development innovation treatment strategies for these tumors that are traditionally difficult to manage with conventional radiation itself.



EXPLORING THE ROLE OF DNA DAMAGE RESPONSE TO IONIZING RADIATION

DNA double-strand breaks (DSBs) constitute the most dangerous type of DNA damage induced directly by ionizing radiation. The ability to sense DSBs and activate DNA damage response (DDR) pathways is crucial for maintaining genomic integrity and cell viability. There are two major pathways involved in the repair of DSBs, namely non-homologous end-joining (NHEJ) and homologous recombination (HR). Over the past decades, a series of studies have identified a biological phenomenon termed radiation-induced bystander effect or abscopal effect, wherein directly irradiated cells transmit DNA damage signals to non-irradiated cells thereby inducing a response similar to that of irradiated cells, e.g. the generation of DSBs. Although the bystander effect has been well described, the mechanisms of this process remain to be fully elucidated. While recent studies have provided mechanistic insights into a cytosolic DNA sensing system, the cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) synthase (cGAS)-STING pathway, as the major link between DNA damage and innate immunity, the roles of radiation-induced cytosolic DNA and its sensing in the bystander or abscopal effect have not been well explored.

NBS1 AND H2AX COMPLEMENT EACH OTHER IN DNA DAMAGE RESPONSE

Principal Investigator:

Jinsong Yuan, MD, PhD,
Assistant Professor of Radiation Oncology (in the Center for Radiological Research) at CUIMC

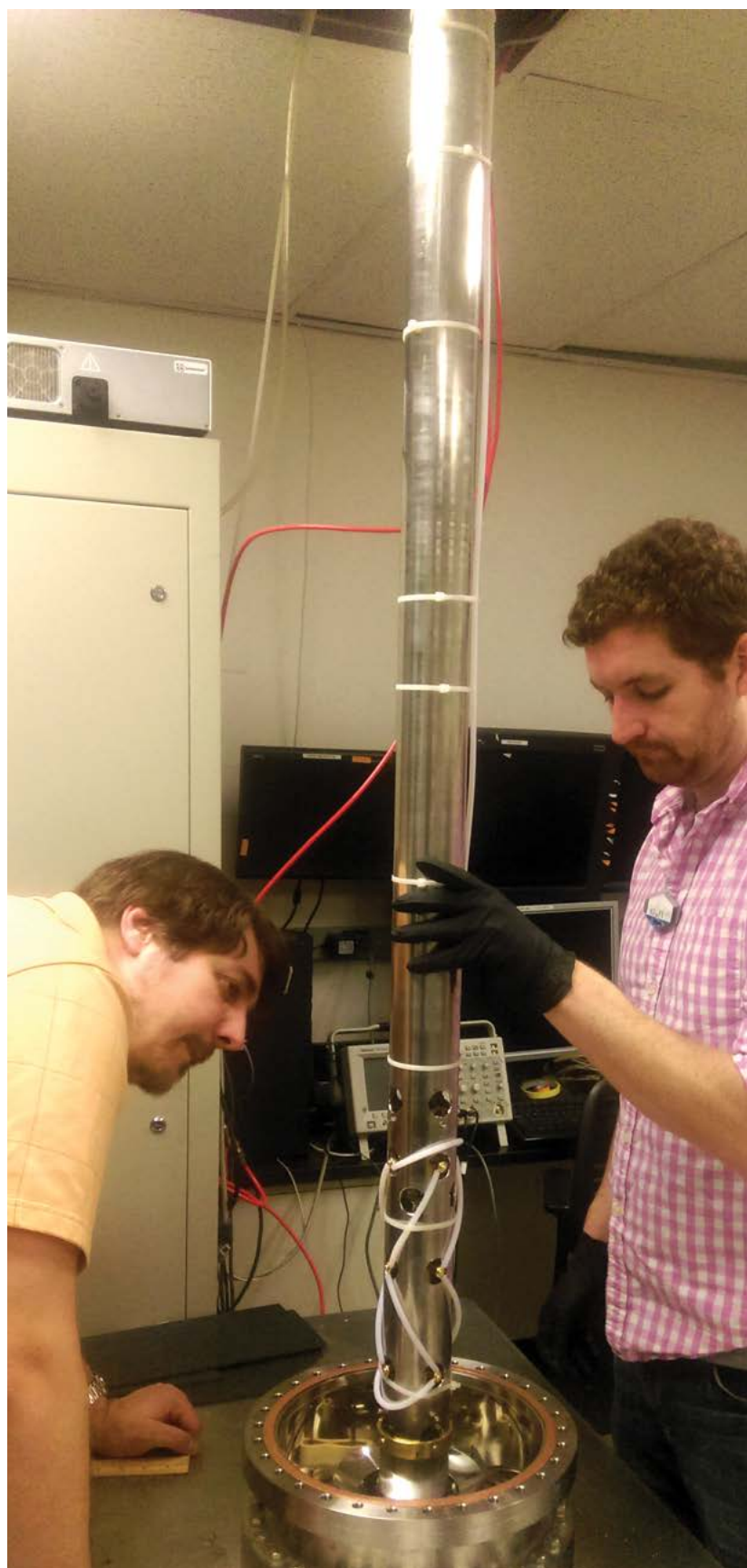
Collaborators (at other Institutions):

Drs. Wenqi Wang, PhD,
(University of California Irvine) and Junjie Chen (The University of Texas MD Anderson Cancer Center)

Dr. Yuan's central hypothesis is that the cytosolic DNA and its sensing system are critical for DSB induction in bystander cells and play important roles in radiation-induced tumor immunogenicity, secondary tumors and normal tissue toxicity. In response to DSBs, phosphorylation of histone variant H2AX at serine 139 creates γ H2AX, which is a key event in DNA damage response. However, Dr. Yuan, his collaborators and others showed that the MRE11-RAD50-NBS1 (MRN) complex can act independently of the H2AX-mediated DDR cascade to promote DNA end resection, which is critical for homologous recombination repair. In this project, they started with the

successful generation of a number of NBS1-null human somatic cell lines, which indicate that NBS1 is dispensable for the survival of human somatic cells. They further demonstrated that NBS1 is required for cell survival when cells encounter S phase specific DSBs. More interestingly, using an inducible reconstitution system in NBS1-null and H2AX-null cell lines, they were further able to generate cellular models with double knockout of NBS1 and H2AX. They conclude that double knockout of NBS1 and H2AX is synthetic lethal in human cells, which strongly supports their hypothesis that the NBS1-dependent initial recruitment and H2AX-dependent stable accumulation of DDR signaling components complement each other and are required for DNA repair and cell survival. The identification of NBS1 and H2AX as a novel pair of synthetic lethal genes will help shed light on not only research in the field of DNA damage repair but also new directions for cancer therapy. They anticipate that this synthetic lethality paradigm can be potentially expanded from NBS1 and H2AX to MRN complex and H2AX/MDC1 signaling axis.

Given that various inhibitors of DDR components are now in preclinical and clinical development, a thorough understanding of DDR pathway complexities is urgently needed to fully exploit the potential of DDR inhibitors and to ensure their long-term clinical success. Dr. Yuan's studies will reveal the detailed mechanisms underlying H2AX-independent DDR signaling. The knowledge gained here will not only elucidate the molecular details about how DNA damage is detected or sensed in the first place, but will also provide the rationale for exploiting the synthetic lethal interaction between two DDR pathways for treating cancer patients with selective DDR inhibitors, especially when they are combined with radiation therapy.





THE ROLES OF FIGNL1-C1ORF112 (FLIP) PROTEIN COMPLEX IN HOMOLOGOUS RECOMBINATION REPAIR

Principal Investigator:

Jinsong Yuan, MD, PhD,
Assistant Professor of Radiation Oncology (in the Center for Radiological Research) at CUIMC

Collaborators at CRR:

Dr. Tom K. Hei

Collaborator (at the University of Hong Kong):

Dr. Michael S.Y. Huen

Inheritance of mutations in one of the breast cancer susceptibility genes, *BRCA1* or *BRCA2*, is the most significant risk factor for developing breast cancer. *BRCA1* and *BRCA2* are known to function in a common DNA repair pathway, named homologous recombination (HR), which is an essential DNA repair process that uses the homologous sister chromatid to carry out accurate repair of DNA double-strand breaks (DSBs), predominantly taking place during S and G2 phases of the cell cycle. However, while *BRCA1* and *BRCA2* are frequently mutated

in familial breast cancers, mutations of these tumor suppressors are rare in sporadic breast cancers, raising the possibility that other genes involved in the HR repair pathway, but not *BRCA1* or *BRCA2*, may be mutated or dysregulated in sporadic breast cancers. HR deficiencies are frequently present in sporadic breast cancers (defined as a BRCAness or BRCA-like profile).

To better understand the function of HR defects in sporadic breast cancer development, scientists and the medical community at large have to know more about the HR pathway by identifying novel HR factors other than the known *BRCA1* and *BRCA2* tumor suppressors. The *BRCA2*-interacting protein, RAD51 recombinase, is critical for the repair of DSBs via HR to maintain genomic stability. Dr. Yuan and his collaborators previously identified a RAD51-binding protein fidgetin-like 1 (FIGNL1) which is required for efficient HR repair. However, the mechanisms underlying FIGNL1-mediated HR repair are still unclear and need to be elucidated. In this project, Dr. Yuan identified a previously uncharacterized protein, *C1orf112*, as a binding partner of FIGNL1. He found that *C1orf112* and FIGNL1 are mutually interdependent for their stability and cellular localization. Interestingly, further analysis revealed that while *C1orf112* and FIGNL1 are not required for the loading of RAD51 onto single-stranded DNA, they promote the removal of RAD51 from DNA after successful strand invasion, thereby allowing HR-associated DNA synthesis. Dr. Yuan and his team are now investigating the mechanism by which FIGNL1 protein complex promotes the RAD51 dissociation.

This project focuses on identifying a set of new RAD51-associated HR factors, including FIGNL1 and *C1orf112*, and testing their potential roles in breast cancer development and treatment. Dr. Yuan's study is expected to generate important knowledge for understanding breast cancer etiology, which may have great implications for the clinical management of breast cancer patients.



INFECTIOUS DISEASE

Despite improvements in operating practices to ensure clean surgeries, surgical site infections still cause thousands of deaths each year, mainly due to antibiotic-resistant bacteria. The CRR is at the forefront of the development of new UV light techniques to kill drug-resistant microbes, such as MRSA, without harming humans. Our researchers developed the Differential Ultra-Violet Sterilizer (DUVS), a cost-effective technology that uses UV light with a wavelength of 222 nanometers (nm) to kill drug-resistant bacteria during surgery. This approach also has potential for reducing the spread of viral infections in public spaces. Scientists within the CRR are continuing to test the efficacy and safety of far-UVC light (207–222 nm) on humans. This section includes a summary of research that explores variants of the DUVS approach.

DIFFERENTIAL ULTRAVIOLET LIGHT STERILIZATION (DUVS)

Principal Investigator:

David J. Brenner, PhD, DSc,
*Higgins Professor of Radiation Biophysics
(in Radiation Oncology) and of Environmental
Health Sciences*

Collaborators (at Columbia):

Drs. David Welch, Manuela Buonanno,
Henry Spotnitz, and Gerhard Randers-Pehrson

Collaborators (at the California Institute of Technology NASA Jet Propulsion Laboratory):

Mr. Arman Seuylemezian and Ms. Lisa Guan

Dr. Brenner and his collaborators are investigating using far-UVC light (in the range of 207–222 nm) to kill pathogens such as bacteria and viruses without harming human cells. While other wavelengths of UV light are hazardous to human health, the biophysical limitations on far-UVC light penetration suggest it's safe for human exposure. Dr. Brenner's results show far-UVC light has all the anti-microbial advantages of conventional germicidal UV light (at 254 nm), but without the safety hazards. Studies on efficacy and safety are ongoing in the following areas: Prolonged Safety Studies: The foreseen use of continuous exposure to far-UVC as a means to prevent disease transmission in hospitals or public spaces requires testing for safety concerns. In an ongoing 60-week experiment, Dr. Brenner and his colleagues are exposing mice to far-UVC for 40 hours per week and monitoring for both eye and skin damage. Testing is scheduled to conclude in late 2020.

Safety studies are also ongoing in the potential application of far-UVC technology to prevent infections around medical equipment, such as catheters, which must pass through the skin of a patient as well as clinical applications. Dr. Brenner and his colleagues are working with the NASA Planetary Protection Team to explore the use of far-UVC to help maintain microbial cleanliness during spacecraft assembly.

SPACE RADIATION



Compared to ionizing radiation exposures on Earth, astronauts are exposed to potentially higher levels of radiation (mainly protons, HZE particles, and neutrons) from galactic cosmic sources, periodic solar flares and trapped radiation belts surrounding our planet. NASA is concerned about the acute and long-term health effects of such exposures to crews during long-term manned space flight. Because of the unique nature of space radiation, it is difficult to reduce exposure by shielding and impossible to eliminate entirely. Efforts to assess radiation risks in space have been further complicated by unknowns regarding the combined biological effects of these radiations and the difficulty in reproducing them in a controlled environment on Earth. This section includes summaries of research focused on space radiation at CRR.

A DETERMINATION OF BIOACTIVE PROTEINS SECRETED BY THE HUMAN VASCULATURE IN RESPONSE TO LOW DOSE SPACE RADIATION

Principal Investigator:

Peter Grabham, PhD
Assistant Professor of Radiation Oncology (in the Center for Radiological Research) at CUIMC

Collaborators:

Dr. Lewis Brown and Dr. Afshin Beheshti

Dr. Grabham's research seeks to determine the proteins that are released into the blood by the lining of the human vasculature in response to exposure to space radiation. This would create a useful database for studies of proteins secreted in an astronaut's blood. The microvasculature permeates all tissues and the whole body is a target for space radiation. Studies on the effect of space radiation on human 3D microvessel models show that both developing and mature microvessels lose structure and function after exposure to very low doses of various charged particles. The low fluence of these doses indicates a bystander effect where the response is transmitted to

other cells by secretion of molecules from the target cell. Dr. Grabham proposes to use proteomics to determine the proteins secreted by the human microvessel models in response to Galactic Cosmic Radiation (GCR).

Dr. Grabham and his team have successfully developed dose response curves for each type of radiation and the relative biological effect of GCR is around 10 for each condition. Additionally, they have identified the proteins secreted by the endothelial cells during angiogenesis and in mature human 3D microvessel tissue models in response to radiation. These samples are now ready for proteomic analysis; Dr. Grabham's collaborator, Dr. Lewis Brown, at the Quantitative Proteomics and Metabolomics Center at Columbia will be analyzing the proteomics.

Dr. Grabham is also collaborating closely with Dr. Afshin Beheshti at the National Aeronautics and Space Administration on the following two research projects: "miRNA signature detection and countermeasures against HZE radiation exposure for tissue degeneration" and

"Circulating miRNAs Provides Systemic Host Response to Microgravity: Utilizing GeneLab datasets to identify molecular targets for spaceflight studies."

EDUCATION, TRAINING & OUTREACH



Howard B. Lieberman, PhD

*Professor of Radiation Oncology
(in the Center for Radiological
Research) and Environmental
Health Sciences*



Manuela Buonanno, PhD

Associate Research Scientist

Many CRR faculty members are involved in teaching radiation biology at Columbia, principally through the Radiation Biology course for Radiation Oncology Residents directed by Dr. Sally Amundson. Within this course, Dr. Guy Garty teaches the physics-related sections, and Drs. Sally Amundson, Constantinos Broustas, Manuela Buonanno, Shanaz Ghandhi, Peter Grabham, Helen Turner, and Jingsong Yuan teach topics related to the molecular, cellular, tissue, and clinical aspects of radiation biology.

We are pleased to highlight **Howard Lieberman** and **Manuela Buonanno** because their work aims to reach students in secondary education to encourage and prepare them to pursue careers in science and radiation. Dr. Lieberman is a member of the Advisory Board, Summer Research Program for New York City Secondary School Science Teachers, at Columbia University. This highly competitive program selects New York City high school and middle school science teachers to participate in a two-summer rotation involving hands-on research opportunities in Columbia laboratories. Teachers present their research results in lectures and poster formats to peers; attend seminars, and develop lesson plans for their students based on their experiences in the program.

Manuela Buonanno is an instructor for the Columbia University Science Honors Program. The Columbia University Science Honors Program (SHP) is a Saturday morning program designed for high school students in the 10th through 12th grades interested in science. Dr. Buonanno has taught Radiation Biology for SHP students during the last four years. She is also the editor and curator of the Radiation Research Society (RRS) podcast and vodcasts. Since 2006, she has led a group of volunteer members of the RRS to produce and publish online, open-access audio and video interviews for radiation science professionals. The program includes interviews with authors of articles of interest to the members of the RRS, RRS award winners, and other recordings at conferences, such as round table discussions.



ON THE HORIZON AT CRR

This is an auspicious time at the Columbia University Center for Radiological Research with many exciting new projects on the horizon.

In Spring 2020, CRR scientists will begin pre-clinical studies on FLASH radiotherapy, a new type of radiation therapy delivery system that has great potential to revolutionize cancer treatment by increasing killing of cancer cells with fewer side effects than conventional radiation. Our goal is to understand how FLASH works, in order to harness its capabilities to treat all cancers with fewer side-effects for patients.

In other exciting news, plans are now underway to bolster the energy of the linear accelerator (LINAC) at RARAF. This innovative technology will provide the basis to conduct research using heavy ion radiation to treat intractable cancers, including pancreatic and brain cancers. With our pioneering cancer clinical trials, Columbia's relevant discoveries will move rapidly to improve patient care. We anticipate that our new LINAC installation will be completed in fall 2020.

CRR ADVISORY COUNCIL

The Advisory Council is a volunteer group of professionals dedicated to helping support the CRR's mission to advance radiological sciences research for the ultimate benefit of human health and safety, at home and abroad. The Advisory Council is tasked with developing philanthropic support, guidance, and strategic planning to enable the CRR to best serve the public interest and provide timely, accurate scientific advice to local, state, and national agencies and organizations. Its members are nationally recognized leaders in government, finance, industry, law, public policy, public health, and non-profit management. They include:

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Conservative activist, commentator, author and academic

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The Columbia CRR's ground-breaking research is made possible through the support of public sector grants and private philanthropy. The CRR would like to recognize and thank the supporters below for their contributions in 2019:

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Biomedical Advanced Research and Development Authority (BARDA) / Asell Inc. Subcontract

High-Throughput Biodosimetry after Radiological and Nuclear Events

Defense Advanced Research Projects Agency (DARPA)

A Multimodal Oral Non-viral CRISPR-Cas Medical Countermeasure to Enhance Ionizing Radiation Resilience and Survival

National Aeronautics and Space Administration (NASA)

Physical and Biological Modulators of Space Radiation Carcinogenesis

A determination of bioactive proteins secreted by the human vasculature in response to low dose space radiation

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Retrospective estimation of protracted radiation doses using radiation-responsive biomarkers in human lymphocytes

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Department of Defense

Targeting MEK5 Enhances Radiosensitivity of Human Prostate Cancer and Impairs Tumor-Associated Angiogenesis

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