Special Research Edition—Highlighting Basic Science Research in Radiation Oncology

Division of Radiation Cancer Biology

Insider Reveals Amazing Details about the Shen Laboratory

DNA repair, homologous recombination, Cell cycle checkpoint, Maintenance of genomic stability, Modulation of cellular sensitivity to therapeutic DNA damage ... these are a few of the favorite things of the Shen Lab.

Zhiyuan Shen, MD, PhD, Associate Professor and Chief of the Division of Radiation Cancer Biology, currently has a number of funded research projects examining these issues.

His laboratory staff are Jingmei Liu, Research Teaching Specialist I; Huimei Lu, RA; Cosimo Antonacci, Post Doc; Jingyin Yue, Graduate student; Jinjiang Fan, Graduate student; and Yanying Huo, Post Doc and Yi-Yuan Huang, Graduate student.

The following details surrounding the research activities of the Shen lab uncover the amazing scientific secrets on the brink of discovery.

Maintenance of genomic stability and prevention of tumorigenesis by precisely regulated homologous recombination (HR) - Genomic instability is a major driving force for tumorigenesis. Mammalian cells use several mechanisms to maintain their genomic stability, including high fidelity DNA replication in S-phase, accurate chromosome segregation in M-phase, precise and error-free repair of DNA damage throughout the cell cycle, and precise cell cycle coordination. HR often precisely repairs DNA double strand breaks, and restarts stalled replication forks to ensure the fidelity of DNA replication and to enable accurate chromosome segregation in mitosis. Thus mis-regulation of HR is a major source of genomic instability. At least four types of HR mis-regulation may occur:

4 types of HR mis-regulation
- HR often uses a sister-chromatid (or a highly homologous region) as the template for DNA repair, and is historically considered an error-free DNA repair pathway. When HR is inhibited, cells may use alternative repair pathways that are more error-prone. Thus, reduced HR is considered a risk factor for tumorigenesis.
- HR DNA intermediates may increase product errors, leading to genomic instability.
- On the other hand, non-restricted HR may enable recombination between similar sequences, such as repeat sequences of the human genome. This increases the risk of regional chromosome rearrangements, which is a form of genomic instability.
- HR is highly coordinated with other cellular processes such as DNA replication, mitosis, and cell cycle regulation. Mis-coordination of HR with cell cycle is expected to be a major source of HR-related genomic instability.

We are interested in how HR is regulated, and coordinated with other cellular processes such as cell cycle regulation and mitosis. We address this issue by examining the functions of proteins that may regulate both HR and cell cycle control. One such protein is BCCIP (BRCA2 and CDKN1A Interacting Protein). Our works have shown that BCCIP regulates HR, cell cycle, and mitosis. Alterations of BCCIP have been implicated in many forms of human cancer. Currently, biochemical, cell and molecular biology, and transgenic approaches are being used to further characterize BCCIP functions and biochemical activities, and its roles in...
Special Research Edition—Highlighting Basic Science Research in Radiation Oncology

Research in the Division of Radiation Physics

Radiosurgery planning

Behind the scenes of the Yue Laboratory
Ning J. Yue, Ph.D., joined the department in 2006 as Professor and Vice-Chair of Radiation Oncology and Chief of the Division of Radiation Physics. He is a permanent fixture on the clinic scene where he is QA king. But behind the scenes, unknown to many, Dr. Yue pursues his passion for applied physics. The following is his first hand acknowledgement of the exploits of his jolly band of researchers.

1. Gated Radiation Therapy Based on Registration of Fluoroscopy and 4D Computed Tomography

The objective of this project is to develop a radiation beam gating technology that is based on the motion information of the target volume directly tracked with the dynamic texture recognition and registration between fluoroscopy and 4D computed tomography. It is proposed to exploit recent advances in dynamic texture recognition and image registration between fluoroscopy and 4D computed tomography (4DCT) to directly track the moving target volume. The directly tracked motion information of the target volume will be used to determine the gating parameters of radiation treatment beams as well as patient setup verification parameters.

This project has been conducted collaboratively with Dr. Metaxas’ Group at the Center for Computational Biomedicine, Imaging and Modeling and the Department of Biomedical Eng. and Computer Science.

The project team members are:
Ning J. Yue, Ph.D., CINJ, UMDNJ – Robert Wood Johnson Medical School
Dimitris Metaxas, Ph.D., Rutgers University
Bruce G. Haffty, M.D., CINJ, UMDNJ – Robert Wood Johnson Medical School
Sukmoon Chang, Ph.D., Penn State University
Sung Kim, M.D., CINJ, UMDNJ – Robert Wood Johnson Medical School
Salma K. Jabbour, M.D., CINJ, UMDNJ – Robert Wood Johnson Medical School
Jinhao Zhou, M.S., Rutgers University

2. Development of a Deformable Model-based Registration Algorithm in Prostate Radiotherapy

The objective of this project is to develop a deformable model-based prostate registration algorithm to potentially improve the quality of prostate radiotherapy, and to potentially improve the feasibility of adaptive radiotherapy.

In order to deliver conformal and precise radiation dose to the target volume of the prostate in external beam radiotherapy, advanced imaging tools with the state of the art radiation delivery technologies, such as 3D CRT and IMRT, have widely been used. These methods depend on the precise and fast delineation and registration of the target volume between the planning and the treatment images. However, most existing methods perform the registration relying on rigid pelvic bony landmarks or fiducials, ignoring the prostate itself. In this project, a novel and accurate registration method is proposed and developed based on soft tissue, i.e., prostate, to capture the transformation between the planning and treatment CT images for external beam radiotherapy, so that treatment accuracy can be potentially improved.

This project has been conducted collaboratively with Dr. Metaxas’ Group at the Center for Computational Biomedicine, Imaging and Modeling and the Department of Biomedical Eng. and Computer Science.

The project team members are:
Ning J. Yue, Ph.D., CINJ, UMDNJ – Robert Wood Johnson Medical School
Dimitris Metaxas, Ph.D., Rutgers University
Bruce G. Haffty, M.D., CINJ, UMDNJ – Robert Wood Johnson Medical School
Sukmoon Chang, Ph.D., Penn State University
Sung Kim, M.D., CINJ, UMDNJ – Robert Wood Johnson Medical School
Salma K. Jabbour, M.D., CINJ, UMDNJ – Robert Wood Johnson Medical School

3. An Optimization Strategy to Compensate For Rotational and Deformable Target Deviations with Translational Corrections in Image Guided Radiotherapy

The objective of this project is to develop a strategy to optimize the translational corrective shifts to compensate for rotational and deformable deviations in image guided radiotherapy (IGRT).

The utilization of various IGRT technologies improves the detection of temporal and spatial deviations of the target volume relative to planned radiation beams. With the aid of these IGRT technologies, it becomes possible to identify the target volume at the radiation treatment stage. However, since components of the detected deviations may be translational, rotational and deformable, question remains whether the simple treatment couch translational movement can be optimized to compensate for these complicated deviations. The issue is further complicated by the fact that the deviation of the target volume and the corrective movement of treatment couch may also cause change of target depth relative to planned beams, leading to dosimetry change from the corresponding treatment plan. In this study, an optimization strategy is proposed and developed to investigate the issue and answer the above question. The optimization process involved the utilization of the Hill Climbing algorithm, the planned dose distribution, and the detected target volume.

The project team members are:
Ning J. Yue, Ph.D., CINJ, UMDNJ – Robert Wood Johnson Medical School
Bruce G. Haffty, M.D., CINJ, UMDNJ – Robert Wood Johnson Medical School
Sung Kim, M.D., CINJ, UMDNJ – Robert Wood Johnson Medical School
Salma K. Jabbour, M.D., CINJ, UMDNJ – Robert Wood Johnson Medical School
Venkat Narra, Ph.D., UMDNJ – Robert Wood Johnson Medical School
Brett Lewis, M.D., Ph.D., CINJ, UMDNJ – Robert Wood Johnson Medical School
Sharad Goyal, M.D., CINJ, UMDNJ – Robert Wood Johnson Medical School

Clinic Update
Interim Director is Appointed

The department appointed Shushma Patel, RTT as Interim Director of Radiation Oncology. Shushma has been a member of the department since 2003, and was most recently the Assistant Chief Radiation Therapist. Shushma brings many years of experience and an outstanding work ethic to the role. She has already begun to implement best practices to improve our clinical service. Keep up the good work!
Division of Radiation Cancer Biology

XIA Confidential

The Never Before Told True Story of the Xia Laboratory

Dr. Jianglin Ma (left) and Dr. Hong Cai (right) unlocking the secrets behind the role of PALB2 in DNA repair

Bing Xia, PhD, Assistant Professor of Radiation Oncology, joined the department in the fall of 2007. Since coming on board, Dr. Xia and the members of his lab have labored tirelessly to examine the role of PALB2 in DNA repair. The following information released by Dr. Xia reveals for the first time the awe-inspiring potential of the work in his laboratory.

Background

Dr. Xia’s lab is investigating the functions and mechanisms of BRCA1, BRCA2, and PALB2, a major BRCA2 partner protein that links BRCA1 and BRCA2 to form the “BRCA pathway.” All three proteins are key players in the DNA damage response and critical for the suppression of breast cancer. In addition, BRCA2 and PALB2 are also critical for suppression of Fanconi anemia (FA), a genetic childhood syndrome characterized by birth defects, progressive bone marrow failure (anemia), and cancer susceptibility. FA patients with BRCA2 or PALB2 deficiency have severe phenotypes featuring the development of “embryonal” cancers such as medulloblastoma and Wilms tumor at very young ages.

Research Areas

The lab is working on the following research themes:

1) Biochemical purification of the BRCA2/PALB2 complexes under different conditions and in different cell types, aiming to identify more players and reveal the dynamics and potential tissue specificity of the BRCA pathway;

2) Structure-function analysis of BRCA1, BRCA2 and PALB2;

3) PALB2 knockout mouse model;

4) Identification and validation of clinically relevant BRCA2 and PALB2 mutations in collaborations with human genetics groups; and

5) Searching for genes in the BRCA pathway that may serve as new biomarkers for rational drug intervention and radiation therapy. Through above studies, we aim to discover the link(s) between the molecular actions of these proteins in the DNA damage response and their abilities to suppress tumorigenesis, and hopefully contribute to the clinical management and/or treatment of aforementioned diseases.

Team

Current members of the Xia lab include Dr. Jianglin Ma, a postdoctoral fellow, and Dr. Hong Cai, who is an RTS IV. Dr. Ma works on the biochemical purification of PALB2 protein complexes, the identification of additional players in the pathway, and the functional connection between BRCA1, PALB2, and BRCA2. Dr. Cai works on the structure-function analysis of BRCA2, the purification of BRCA2 protein complexes, and the PALB2 knockout mouse model.

For more information about Dr. Xia and his research interests, see related story on page 4, Meet the Players.

Shen Lab (cont. from page 1)

tumorigenesis.

Modulation of cell response to therapeutic DNA damage - Upon DNA damage, three potential outcomes are expected: cell death, survival with full recovery of damaged DNA, or survival with alternations in the genome. The ultimate goal for DNA damage based cancer therapy is to maximize cancer cell death, minimize death of normal cells, and minimize survival with genomic alterations for cancer and normal cells. These outcomes are dictated by two major factors: 1) the initial level of DNA damage received by each cell type; and 2) an intrinsic network of DNA damage response within the cells. This network of DNA damage response includes signal transduction, gene expression regulation, DNA repair, cell cycle checkpoints, and regulation of cell death pathway. After a comprehensive understanding on the mechanism of action for this network, it is possible to modulate this network to favor cancer cell death, while protecting normal cells. We are interested in developing strategies to modulate the cell responses to DNA damage to increase cancer treatment efficacy while reducing side effects. Cell based screen systems are being developed to identify drug targets and drugs to sensitize cancer to therapeutic DNA damage. We are also interested in identifying markers that may predict clinical outcomes of therapeutic DNA damage.
Meet the players

Bing Xia, PhD
Assistant Professor of Radiation Oncology
Division of Radiation Cancer Biology

Eureka!
Meet Dr. Bing Xia, Boston Red Sox fan (we forgive him, because he doesn’t hate the Yankees) and the discoverer of PALB2. Discoverer of what? The PALB2 protein, or the Partner and Localizer of BRCA2 (the name is approved by the Human Gene Nomenclature Committee), is a major binding protein of the BRCA2 breast cancer “susceptibility” protein. Like BRCA2, PALB2 is one of the keys proteins necessary for homologous recombination, a major mechanism to correctly repair DNA breaks, which can be caused by natural or therapeutic radiations, among others. These genes are also known as “tumor suppressor” genes. Without PALB2 the BRCA2 gene cannot exert its DNA repair and tumor suppressor function within the cell. The result is that cells either die or acquire the ability to grow and divide in an uncontrolled fashion, which leads to tumor formation. The discovery of PALB2 and the role it plays is clearly a significant finding for cancer research, specifically breast cancer research, since mutations in PALB2, like those in BRCA2, are associated with substantially increased risk of breast cancer.

Decisions, decisions, decisions

As a high school student, chemistry came easily to the young Dr. Xia and he excelled in the subject. His exceptional ability allowed him to bypass the national college entrance exams in China and gained him admission to the prestigious Wuhan University. Because he was admitted on the basis of his ability in chemistry, he was asked to select a chemistry major and so he chose biochemistry. Dr. Xia graduated from Wuhan University in 1992 with a Bachelors degree in biochemistry. After working in a biotech company for 4 years, Dr. Xia left China in 1996 to pursue his graduate study in the US. He joined the laboratory of Dr. Masayori Inouye, then chair of the Department of Biochemistry at UMDNJ-RWJMS, and studied the biochemical basis of bacterial adaptation to low temperatures. Upon completion of his Ph.D. study, he wanted to work on something different and decided to study DNA repair and cell cycle regulation in Dr. David Livingston’s laboratory at the Dana-Farber Cancer Institute and Harvard Medical School. It was during his post doctoral fellowship at Dana Farber that Dr. Xia isolated the PALB2 protein and ascertained the key role that it plays in breast cancer tumor suppression.

What next?
After this breakthrough, Bing concluded his fellowship in Dr. Livingston’s lab and accepted a position as Assistant Professor of Radiation Oncology at RWJMS-CINJ. He has continued to expand on his research on PALB2 and BRCA2, with an aim to translate some of his findings into something that may benefits cancer patients. Many people believe that the future of medicine lies in designer drugs, individually tailored drugs that are designed around a patient’s genetic make-up. Understanding the functions of tumor suppressor proteins such as BRCA1, BRCA2 and PALB2, will allow researchers to determine their effects on drug sensitivity. This is done by knocking down or knocking out the target proteins in cultured cells or model animals and then exposing the cells/animals to various drugs to establish drug sensitivity or the ability of the drug to kill the cell. The expectation is that tumor cells of people with mutations in such proteins, which mimic the knockdown/knockout cells, will have similar drug sensitivity. Studies of this nature are complex and can take many years to translate into real therapeutic strategies in humans. Dr. Xia’s lab has begun the process and if past performance is an indicator of future performance, we’re in luck.

All work and no play makes Jack a dull boy

Dr. Xia believes that if you do experiments well, you will cook well. Bing’s experimental track record is pretty good, so we are guessing that his cooking is even better. He cooks often and especially enjoys cooking (and eating) Chinese dishes. His specialty is broiled pork belly, which his 8-year old son loves. Beyond cooking, Bing’s artistic credentials are almost as impressive as his academic credentials. Back in China, he often sang Kara OK and went to ballroom dancing parties. These talents were put on the back burner for many, many years while Bing pursued his studies in this country, during which there was no time for anything else. But now, he can exhale slightly. Dr. Xia, his wife and their son reside in Highland Park where they have recently purchased a home. Last weekend, Bing pruned his first tree and bought a lawnmower. He is looking forward to gardening in his new yard for the first time. And let’s hope that he will to be able to resume ballroom dancing again, sometime soon.

~End.
Quick Primer on UMDNJ Travel Policy - Don’t Leave Home Without Reviewing It!

All Radiation Oncology UMDNJ employees (both faculty and staff) are required to familiarize themselves with the details of the UMDNJ Travel Policy. Lack of knowledge of the Travel policy does not constitute grounds for an exception to the policy. This primer is intended to supplement the policy, not replace it. Employees are strongly advised to consult with administrative staff prior to a trip to ensure that they understand what expenses are permitted by University policy. For a copy of the University Travel Policy please visit the following website: http://www.umdnj.edu/oppmweb/Policies/HTML/financial/00-01-50-10_00.html

1) Travel Advance—Always required. A properly completed Travel Advance will ensure smooth and timely reimbursement. Complete the report to reflect ALL categories with relevance: transportation (including car rental, taxi or mass transit), lodging, meals, registration fees, parking, etc. Estimate costs as accurately as possible taking into account geographical differences. If any category exceeds University guidelines (for example, lodging in excess of $100/day) an exception must be requested and approved by Director of CINJ. Certain Ethics forms may also be required.

2) Travel Expense—Always required. Provide receipts and itemize all expenses. Do not submit reimbursement for expenses that exceed University guidelines unless an exception was granted on the travel advance—it will not be approved by the department unless traveler can provide documentation explaining the need to exceed University guidelines and the reason that permission was not acquired via the Travel Advance.

3) University guidelines:
   - Lodging—cannot exceed $100 per day
   - Meals—Breakfast $9. Lunch $11, Dinner $25. These rates include sales tax and gratuities.
   - Transportation—air travel must be in coach class, train travel must be economy or lowest fare
   - Personal charges—not reimbursable. These include, but are not limited to, alcoholic beverages, laundry, valet service, and entertainment fees.
   - Telephone—one call per day to immediate family is reimbursable when traveling out of town.
   - Registration Fees—reimbursable
   - Baggage handling fees—not reimbursable
   - Gratuities—reimbursable within reasonable market rate. Total daily lodging plus meals plus gratuity plus tax may not exceed $145 per day.
   - Car rental—reimbursable when the cost of the rental is less than the overall cost of other reasonably accessible means of transportation. Liability insurance should be included for the rental.

Travel FAQs

Q. I will be attending a conference at a resort in the South of France. I have never been there before. Am I allowed to bring my spouse/significant other on the trip with me?
A. Yes, your spouse/significant other may travel with you but any additional charges associated with their travel, such as airfare, room fees, food etc., may not be reimbursed with University funds.

Q. My conference in Florida ends Thursday morning. I’ll be going on a cruise that departs from Florida on Friday. Will the room charge for Thursday be reimbursed?
A. No. The University will not cover lodging expenses for an overnight stay if the conference that you are attending concludes in the morning.

Q. Do I need to complete a travel advance/expense report if I will be traveling in scholarly capacity where the sponsor is covering these expenses of the trip?
A. Yes. Travel advance and expense reports are required in order to ensure that you have University approval for the trip so that relevant University insurance coverage is in place in the event of unforeseen circumstances.

Q. I am sharing a room with my colleagues, but the reservations and the bill will be in my name. My colleagues will pay me their share of the lodging expense. How do I ensure that they are reimbursed?
A. You and your colleagues need to make sure that each of you submits a travel advance and document the sharing arrangement on the advance. Additional paperwork, such as a memo from you, may be required when your colleagues submit their travel expense reports.
As Radiation Oncology’s outgoing first Chief Resident, Dr. Sharad Goyal has done a tremendous job and the department recognizes and congratulates him on his successful tenure!

Dr. Goyal has been instrumental in organizing the department for future residents, and to a large extent, setting up the residency program. He has been an integral part in establishing the clinical didactic, physics, radiobiology lecture schedules, the residency handbook (which outlines expectations and bylaws of the program), and developing the infrastructure of the program such as the call schedule and weekly conference.

Dr. Goyal leaves behind his resident days to assume a faculty position in the department as Instructor. Drs. Brett Lewis and Matthew Poppe will serve as co-Chief Residents for the next academic year. In addition, the Department of Radiation Oncology will be welcoming 2 new residents on July 1, 2008: Amar Rewari, MD, MBA and Rahul Parikh, MD.

More to come about them in a future edition of The Beam.

Residents will continue the current rotation schedule through July 4, 2008.

The team format is as follows:
- Team A - Drs. Haffty & Gabel, Dorothy Pierce, Matt Poppe
- Team B - Drs. Khan & Cohler, Jayne Camporeale, Brett Lewis
- Team C - Dr. Jabbour & Sabin Motwani; Dr. Kim & Parima Darou

Presentations:
- Atif Khan, MD
  American Brachytherapy Society Meeting. Local control, toxicity, and cosmesis in women younger than 50 enrolled on the American Society of Breast Surgeons MammoSite registry trial. Boston, MA. May 2008
- Bruce Haffty, MD

Applications:
- Zhiyuan Shen, MD, PhD, PI. Filamin-A as a Novel Marker and Target for Breast Cancer Metastasis. DOD, Total $585,000. May 2008
- Bing Xia, PhD, PI. Defining the Composition and Dynamics of the BRCA1-PALB2-BRCA2 Breast Cancer Protein Network. DOD, Total $585,000. May 2008

Publications:
THE DEPARTMENT OF RADIATION ONCOLOGY AT UMDNJ - RWJMS AND CINJ AND RWJUH

Bruce G. Haffty MD
Professor and Chair

Clinical Radiation Oncology
- Molly Gabel, MD
  Associate Professor and Chief, Clinical Radiation Oncology
- Alan Cohler, MD
  Instructor
- Salma Jabbour, MD
  Assistant Professor
- Atif Khan, MD
  Assistant Professor and Associate Director, Residency Training Program
- Michael McKenna, MD
  Assistant Professor

Residents
- Sharad Goyal, MD
  Chief Resident PGY-5
- Brett Lewis, MD, PhD
  PGY-3
- Matthew Poppe, MD
  PGY-3
- Parima Daroui, MD, PhD
  PGY-2
- Sabin Motwani, MD
  PGY-2

Radiation Physics
- Ning Jeff Yue, PhD
  Professor, Vice Chair and Chief, Radiation Physics
- Satish Jaywant, PhD
  Associate Professor
- Venkat Narra PhD
  Associate Professor

Advance Practice Nurses
- Jayne Camporeale, RN, MSN, APN
- Dorothy Pierce, RN, MSN, APN

Clinical Services at RWJUH
- Shushma Patel, RTT
  Interim Director
- Jisseelle Nater
  Operations Manager
- William Witherup
  Chief Therapist
- Ann Marie Maisel
  Therapist
- Susan Resavy
  Therapist
- Mary Kazio
  Therapist
- Krystin Greene
  Therapist
- Melissa Mareth
  Therapist
- Lillian Hosein
  Therapist
- Carrie Strauss
  Therapist
- Kevin Finn
  Therapist
- Scott Barnes
  Chief of Dosimetry
- Rihan Davis
  Dosimetrist
- Jacqueline Tull, RN
  Nurse
- Theresa Singley, RN
  Nurse
- Barbara Lee, RN
  Nurse
- Brenda Adell
  Medical Coder
- Terry Blekeski
  Senior Medical Coder
- Shelly Muhammad
  Clerical Coordinator
- Gladys Torres
  Medical Biller
- Azalia Laguna
  Clerk
- Melissa Morales
  Clerical
- Tanya Sharpe
  Receptionist
- Fatimah Ahmed Alfaraj
  Visiting Researcher

Radiation Cancer Biology
- Zhiyuan Shen, MD, PhD
  Associate Professor and Chief, Radiation Cancer Biology
- Bing Xia, PhD
  Assistant Professor
- Jingmei Liu
  Research Teaching Specialist I
- Huimei Lu
  Research Teaching Specialist III
- Jingyin Yue
  Graduate Student
- Jinjiang Fan
  Graduate Student
- Yi-Yuan Huang
  Graduate Student
- Devora S. Schiff
  Research Teaching Specialist III
- Jianglin Ma
  Post Doctoral Fellow
- Cosimo Antonacci
  Post Doctoral Fellow
- Hong Cai
  Research Teaching Specialist IV
- Yanying Huo
  Post Doctoral Fellow

Academic Administration at RWJMS and CINJ
- Sharda Kohli, MBA
  Clinical Department Administrator
- Jo-Ella McClinnon
  Management Assistant
- Odalis Sanchez
  Secretary I
- Rosa Schweighardt
  Secretary II
- Rhonda Lyles
  Secretary II

Contact Us
On the web at:
http://www2.umdnj.edu/raoncweb/index.htm
Admin/Research/Education at CINJ:
Department of Radiation Oncology
The Cancer Institute of New Jersey
Room 2038
195 Little Albany Street
New Brunswick, NJ 08901
Phone: 732-235-6181

Clinical Services at RWJUH:
Department of Radiation Oncology
G2 Level
One Robert Wood Johnson Place
New Brunswick, NJ 08901
Phone: 732-253-3939