How breast cancer originates from normal cells

**Dr. Rumela Chakrabarti** is an assistant professor (tenure-track) in the Department of Biomedical Sciences. Dr. Chakrabarti attended Pune University, India, receiving her B.S. in Zoology in 1999 and an M.S. in Genetics in 2001. She then moved to the United States and received her Ph.D. in Biomedical sciences in 2007 from Kent State University, Ohio, where she studied the function of phosphatases in sperm formation and motility. Being trained as a developmental biologist during her Ph.D., she next joined the State University of New York at

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Buffalo, New York as a post-doctoral fellow where she investigated the function of transcription factors in dictating the cell fate of stem and progenitor cells in mammary gland development. Her successful initial studies on mammary stem cells then inspired her to move to Princeton University, New Jersey for additional postdoctoral training where she extended and integrated her expertise and knowledge in normal mammary gland biology to understand the role of stem cells in breast cancer initiation, progression and metastasis. Dr. Chakrabarti is interested in the fundamental question of how breast cancer originates from normal cells and how molecular events in early tumorigenesis influence the course of disease, including metastatic progression. Additionally, she is interested in how cell signaling between breast cancer cells and their microenvironment dictates the fate of these cancer cells.

Cell fate regulators of normal mammary gland development in breast cancer

Breast cancer remains a major health threat due to therapeutic challenges driven by both its heterogeneity and metastatic recurrence. Genes and signaling pathways that control normal mammary epithelial differentiation influence the formation and evolution of different subtypes of breast cancer. During her postdoctoral work, Dr. Chakrabarti showed that the transcription factor (TF) Elf5, an ETS family TF, is a master regulator for the establishment and maintenance of the luminal epithelial cells in the mammary gland that produce milk during pregnancy (1). Conditional knockout of Elf5 completely abolishes lactation due to reduced differentiation of mature luminal cells, accompanied by an accumulation of luminal progenitors. Dr. Chakrabarti also identified a novel role for Elf5 in inhibiting mammary stem cell activity, thereby promoting luminal differentiation during normal mammary gland development. Notably, these studies identified Elf5 as a key specifier of alveolar fate, acting through direct repression of Notch signaling (2). In addition to demonstrating a role for Elf5 in influencing normal mammary cell fate, Dr. Chakrabarti discovered a novel function for Elf5 in inhibiting the epithelial mesenchymal transition (EMT) that occurs in both physiological and pathological contexts, and plays an important role in metastasis of the basal subset of breast cancers (3). Mechanistically, her group observed that Elf5 expression represses the expression of several EMT-promoting transcription factors, including TWIST1, ZEB1/2, and SLUG. Dr. Chakrabarti is currently determining if Elf5 is also important for earlier changes in breast tumor development and progression using state-of-the art techniques, including conditional knockout mice and lineage tracing Elf5 reporter models. Lineage tracing data and

Meeting Boris Striepen, PhD

In August, Dr. Boris Striepen, professor of microbiology and immunology, joined the Department of Pathobiology. Dr. Striepen studied at the Universities of Bonn and Marburg and received his master’s degree in 1991 and his Ph.D. in 1995. Before arriving at Penn Vet he was a distinguished research professor at the University of Georgia where he worked with the Center for Tropical and Emerging Global Diseases. He also served as director of the Biology of Parasitism summer research course at the Marine Biological Laboratories in Woods Hole. His chief interest is in the cellular and molecular biology of Apicomplexan Parasites with a current focus on the parasite Cryptosporidium, a leading cause of diarrhea and mortality in young children. Dr. Striepen directs an internationally respected research laboratory with support from the National Institutes of Health, the Bill & Melinda Gates Foundation, and others. He and his research group may be found on the 3rd floor, Hill Pavilion.
functional studies suggest that Elf5 functions early during cancer progression and may dictate tumor metabolism (manuscript in preparation). Finally, her recent data suggest that Elf5 functions in a tumor subtype-specific manner to drive either tumor promotion or suppression highlights the need to understand the specific effects of targeted therapy in individual breast cancer subtypes to identify effective chemotherapeutics (Figure 1).

As noted above, Notch signaling is important mammary gland development. However, Notch signaling also drives breast cancer progression and is therefore an attractive therapeutic target. Inhibitors blocking signaling of all four Notch receptors reduce tumor growth, but their broad target specificity and associated gastrointestinal toxicity limits their therapeutic utility. Although therapies targeting specific Notch receptors or ligands are still lacking, preliminary studies from Dr. Chakrabarti’s group indicates that Notch signaling mediated by the ligand Dll1 promotes mammary stem cells activity by interacting with neighboring macrophages through a unique pathway involving Notch-Wnt crosstalk (manuscript under final revision). In breast cancer, her group found that, although Dll1 does not influence basal breast cancer, it promotes luminal breast cancer growth and metastasis, suggesting a unique subtype specific function, which is also dependent on Estrogen signaling (manuscript submitted). Dr. Chakrabarti’s laboratory proposes to use lineage tracing models and knockout mice model to understand the fate of Dll1+ cells in luminal breast cancer and will dissect the mechanistic basis for Dll1-mediated promotion of luminal breast cancer to aid in development of safer ligand based therapy of breast cancer patients.

Recruitment of immune cells by cancer cells in breast cancer

Triple-negative breast cancer (TNBC) represents about 20% of all breast cancers and is a particularly aggressive subtype with increased metastasis and mortality and limited treatment options. Dr. Chakrabarti has previously shown that a transcription factor, ΔNp63 is important for tumor initiation of TNBCs by regulating Wnt signaling and her studies demonstrate that ΔNp63 regulates both normal mammary stem cells and tumor initiating cells in TNBC through regulation of the Wnt receptor Fzd7. Recent studies involving Dr. Sushil Kumar in her group now show that high levels of the transcription factor ΔNp63 are associated with increased metastasis of TNBC. Notably, increased expression of ΔNp63 is associated with increased numbers of myeloid-derived tumor suppressor cells (MDSCs), an immune cell subset associated with tumor progression and metastasis in several cancers including breast cancer. Dr. Chakrabarti’s laboratory found that ΔNp63 promotes
recruitment of MDSCs to the tumor microenvironment by upregulating chemokine expression (manuscript submitted). Moreover, they found that blocking chemokine signaling reduced MDSC recruitment and metastasis, highlighting a novel crosstalk between ΔNp63+ TNBC cells and MDSCs driving tumor progression. Using these findings as a starting point, her lab is currently validating the efficacy of combined immunotherapy/chemotherapy strategies that they hope will improve the prognosis for TNBC patients in the not too distant future.

Dr. Chakrabarti’s research is funded by the NIH/NCI K22 (K22CA193661-01) grant, Breakthrough Bike Challenge award and McCabe award from Abramson Cancer Center. Her laboratory is located in the Hill Pavilion, H432 and her office is in Hill Pavilion H411.

References


**Figure 1.** Elf5 expression in basal and luminal breast tumors respectively. (Left) Immunofluorescent images from lineage tracing mouse model shows Elf5 (GFP⁺) is expressed in many luminal tumor cells which are cytokeratin 14 (K14⁻) supporting oncogene function of Elf5 in luminal tumors. On the right panel, Elf5 (GFP⁺) is expressed in only few basal tumor cells which are K14⁺ (yellow cells), suggesting tumor suppressive function of Elf5.

Dr. Chakrabarti with Sushil Kumar and David W Wilkes

Dr. Sushil Kumar
Student Summer Research at Penn Vet

Students from various programs found their way to a research laboratory during the summer of 2017. Some of the students were participants in the NIH/Boehringer Ingelheim Veterinary Scholars’ program. Some students were part of Penn’s CURF Jumpstart for Juniors research program or the Summer Undergraduate Internship Program (SUlP), designed to provide an intense research experience to students interested in graduate study in the biomedical sciences. Undergraduates from a variety of universities as well as motivated high school students found a laboratory and a mentor where they experienced the world of laboratory and clinical research. Students have a vast selection of laboratories and research topics available to them in the Penn biomedical community. Some of the faculty mentors in the summer research program were: Drs. Gus Aguirre, Montserrat Anguera, Michael Atchison, Narayan Avadhani, Dan Beiting, Charles Bradley, Igor Brodsky, Christine Cain, Raimon Duran-Struuck, Julie Engiles, Hannah Gallantino-Homer, Oliver Garden, Karina Guziewicz, Christopher Hunter, Christopher Lengner, Carolina López, Nicola Mason, Michael May, Kyla Ortved, Michael Povelones, Shelley Rankin, and Hansell Stedman. Whether they were veterinary or medical students, undergraduates, or high school students—these students were inspired to investigate a career in research—basic, clinical or translational medicine. Shown here are some of the student participants.

John Filosa, ’19 is a Penn undergrad in the College of Arts and Sciences and a CURF scholar. He worked with Dr. Michael Povelones on Crithidia fasciculata as a model for insect specific adhesion of trypanosomatids.

Barbara Biney is a Penn undergrad in the College of Arts and Sciences and a CURF scholar. Her research question with Dr. Michael Povelones was: Does the mosquito immune system block heartworm infection in the refractory strain of Aedes aegypti?

Jarui Wang, a student at Peddie High School worked with Dr. Nicola Mason on generating an agonistic anti-CD3 monoclonal antibody for canine T cell activation and expansion.

Shira T Rosenblum, V’20, NIH/Boehringer Ingelheim veterinary scholar, worked with Dr. Hansell Stedman, Perelman School of Medicine, on a Phylogenomic Approach to Design An Optimized µUtrophin for the Treatment of Duchenne Muscular Dystrophy.

Chiara Curcillo, in the NIH/Boehringer Ingelheim (NIH/Boehringer Ingelheim Scholar) summer program, worked with Dr. Igor Brodsky on Defining the protective role of RIPK3 and programmed necrosis in immunity against pathogenic Yersina.

Lindsey Citron, V’19 (NIH/NIH/Boehringer Ingelheim) worked with Drs. Christine Cain and Charles Bradley on characterizing the cutaneous and rectal microbiome of perianal fistulas and the effect of cyclosporine therapy.

Rose Dicovitsky, V’20, (NIH/Boehringer Ingelheim Scholar) worked in Dr. Nicola Mason’s lab on evaluation of the co-stimulatory domain ICOS in CAR T cell therapy for canine B cell lymphoma.

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Save the date:
The Inaugural Penn Vet Cancer Center Symposium

The inaugural Penn Vet Cancer Center Symposium, a two-day event on **November 30th – December 1st, 2017** is open to the Penn community and beyond. The symposium will feature an evening talk from **Cheryl London, DVM, PhD**, research professor, Cummings School of Veterinary Medicine at Tufts University and the Molecular Oncology Research Institute at Tufts Medical Center on November 30th and a full-day scientific symposium at the School of Veterinary Medicine on December 1st, featuring leading experts in comparative oncology and translational cancer studies. The event will be held in 131 Hill Pavilion. To register: [https://www.vet.upenn.edu/cancercentersymposium](https://www.vet.upenn.edu/cancercentersymposium)
Recent Awards

**Robert Greenberg**  
NIH R21  
Discovery of novel antiparasitics that target a pharmacologically atypical schistosome  
Transient Receptor Potential (TRP) ion channel  
7/14/17-6/30/19  $275,000

**Lisa Murphy**  
FDA U18 Competing renewal  
Animal and Animal Food Diagnostic Sample Analysis in Support of FDA Vet-LRN Activities and Investigations  
8/1/17-5/31/22  $191,186

**Oliver Garden (VCIC)**  
Elanco Animal Health  
Collection of Blood Samples from Clinically Normal Dogs as Controls for TCMR0002  
8/23/17-8/23/20  $19,431

**Andrew Vaughan**  
NHLBI/NIH  
Heterogeneity and Bias of Lineage Negative Progenitors in Lung Epithelial Repair  
7/01/17—6/30/20  $459,504

**Andrew Vaughan**  
McCabe Pilot Award  
Single cell fate decisions dictate the quality of lung regeneration  
9/01/17—8/31/18  $22,966

**Camille Syrett (Anguera Lab)**  
NIH General Medical Sciences  
Maintenance of X-chromosome inactivation during B cell development  
9/1/2017 - 8/31/2019  $44,040

**Montserrat Anguera**  
Lupus Fdn of America PhilaTri-State  
Contribution of the Inactive X Chromosome in B Lymphocytes to SLE  
7/1/17-6/30/18  $2000

**Montserrat Anguera**  
University Research FDN  
Penn Vet Next-generation Sequencing Resource 8/1/17–7/31/18.  $11,450

**Marie Eve Fecteau**  
USDA NIFA  
Detection of M avium paratuberculosis in bovine feces using rapid & portable nano pore based sequencer 10/1/17-9/30/18  $26,168

**Christopher Lengner, PhD**  
Associate professor in the Department of Biomedical Sciences, has accepted the role of associate director of the Institute for Regenerative Medicine (IRM). Dr. Lengner has served the IRM in leadership roles throughout his time at Penn, including serving as the head of the Stem Cell Club, participating in IRM search committees, and organizing an IRM retreat.

Publication Highlights


PENN VET HONORS...WORLD Symposium™ announces Mark E. Haskins, VMD, PhD as Recipient of 2018 Roscoe O. Brady Award for Innovation and Accomplishment for his career that spanned over 40 years with a focus on Mucopolysaccharidoses (MPS) and related diseases that are genetic lysosomal storage diseases (LSD) caused by the body’s inability to produce specific enzymes. Dr. Haskins’ leadership in the preservation, development, and elucidation of dozens of large animal models, meant that models were ready to be used to help advance treatment development for patients. The award will be presented at the 14th annual WORLD Symposium, Research on Lysosomal Diseases, on February 5-9, 2018 in San Diego.

Save the date: The 4th Annual Microbiome Symposium will offer a lecture, open to the public, and a conference for the scientific community. The event is hosted by Penn Vet Center for Host-Microbial Interactions (CHMI), Perelman School of Medicine and the Children’s Hospital of Philadelphia. Ed Yong, science journalist and staff writer for The Atlantic, will present a public lecture at 6 pm on November 8, 2017, entitled “I Contain Multitudes: The Microbes Within Us and a Grander View of Life”. The event will be held in Hill Pavilion, room 131. On Thursday, November 9: the Symposium is open to the research community and begins at 8 am—6 pm.

Contact: Dr. Dan Beiting: beiting@upenn.edu with questions
Link: http://www.vet.upenn.edu/research/news-events-conferences/chmi-symposium-2017

Publication Highlights


Center for Host-Microbial Interactions (CHMI)—

Last spring CHMI hosted the 4th transcriptomics course at Penn Vet with 25 students and postdoctoral fellows who worked towards analyzing real RNAseq datasets generated by their laboratories. The course beginning in October 2017 will continue with a focus on the analysis of gene expression data. Daniel Beiting, PhD, Department of Pathobiology, will instruct students in weekly sessions, working with real datasets to carry out data analysis on their laptop computers.

Course website: http://diytranscriptomics.com

The Penn Vet Research Newsletter is distributed quarterly. Suggestions, comments, requests and story ideas may be directed to: resnews@vet.upenn.edu

Phillip Scott, PhD
Office of the Vice Dean for Research & Academic Resources
Editor: Gayle Joseph
University of Pennsylvania
School of Veterinary Medicine
(215) 898-9793