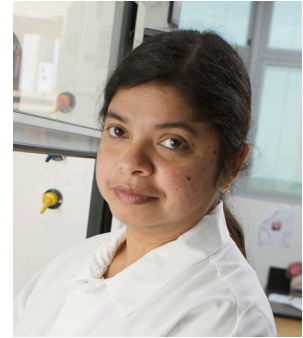


## WOMEN IN CANCER PROFILE

# From physics to cancer biology and everywhere in between



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My father was a Professor of Physics at the Indian Institute of Technology (IIT) Kharagpur, a world renowned engineering school in Eastern India that has produced many famous scientists, engineers and entrepreneurs. Growing up on IIT campus, I felt that the only subjects people studied were either engineering or one of the physical sciences. My mother, who had a degree in nutrition, never worked outside the home – there were no opportunities for individuals with her background. Sure, there were doctors elsewhere in my world – my father's brother was a pediatrician and both my mother's brother and her father were surgeons; but in my high school, biological sciences were for those who hated math. To prove that I liked math and was every bit as smart as my classmates, I decided to major in physics. Not at IIT Kharagpur, of course – that would never do – but at Jadavpur University, known for its engineering school and located in nearby Calcutta (now called Kolkata). This was despite the fact that I routinely did best in my biology classes in high school, likely because my mom tutored me in that subject.

## The physics days

We were required to have two minors; I chose Chemistry and Mathematics. I did reasonably well in my undergraduate classes, finishing towards the top of the class. I learned of Maxwell's equations and Fourier and Laplace transforms; I labored through quantum mechanics and high energy physics; I stayed up all night trying to understand thermodynamics; yet I have now

forgotten most of that material. Later, when my daughter was in high school, I tried to help her with her physics class. Appalled at my lack of knowledge in basic physics, she said 'Ma, are you sure you studied Physics?'

In India, a Master's degree is required in order to go on to a PhD I did my Masters in Physics at Jadavpur University. That year, the department introduced the requirements for an elective subject for each student independent of their track, and a research project. My track was high energy physics, but for my elective, I chose biophysics. For my research project, I applied to work in Dr Papiya Nandy's Biophysics lab.

Dr Nandy's lab changed my outlook on life. The project itself was simple enough: under the guidance of a PhD candidate, Ruma Datta, I was to generate bilayer lipid membranes (BLM) and measure electrical conductivity across the BLM based on a paper she had published the year before ([Datta et al. 1987](#)). The innovation of the work was in the nature of the BLM generated, which was Ruma-di's forte. My job was to generate the BLM and measure its electrical conductivity. I do not think my contribution was enough to merit a publication; however, I relished working in the lab. Being in a lab, I learned, was like being in a club – I was one of them! I wrote an MS thesis on the work at the end of my 2 years. I had done woefully little to show for all the time spent there, but I am happy for what I experienced. I got a taste of how research is conducted and what it means to generate novel data that no one in the world had ever generated before. More importantly, I learned how to interpret new data. For the first time

since I went to college, I genuinely enjoyed what I was doing. I felt that I had earned the gold medal I got for receiving the highest rank in my university's physics master's program.

### The biophysics days

It was Dr Nandy who first suggested that I apply to universities abroad for my PhD. Dr Nandy suggested a few institutions, and I applied to all of them. I was at the time receiving a fellowship from the Council of Scientific and Industrial Research (CSIR), and had saved enough money to pay the application fees for a number of universities. However, I would not be able to support myself in any foreign land, let alone pay tuition. I remember receiving letters of admission from three or four universities, but the language of the letters were such that it sounded like I would be supported from departmental funds for a semester or two and then would have to find an alternate source of funding. At the time, in my naïveté, I assumed it meant that I would have to find an outside job, which my student visa would not allow. (It was much later that I realized that the alternate funding source could be a research or teaching assistantship.) The only university that clearly stated that my stipend, tuition, and related fees would be covered for at least 5 years was the Department of Chemistry of Rensselaer Polytechnic Institute, in Troy, NY, USA. Therefore, I applied for a passport, obtained a student visa, and off to Troy I went!

I landed in JFK Airport in New York on August 20, 1989. This was the first time I had traveled this far alone. Rensselaer Polytechnic Institute (RPI) was the oldest technological research university in the United States, founded in 1824. Dr Ivar Giaever was an alumnus of RPI, and had recently retired from General Electric, in nearby Schenectady. He had shared a Nobel Prize in Physics in 1973, for 'their experimental discoveries regarding tunneling phenomena in semiconductors and superconductors' (Giaever 1960a,b 1974). Now he had returned to RPI as faculty to work on a device he, and his colleague Dr Charles Keese, described as Electric Cell-substrate Impedance Sensor (ECIS). Their website now describes ECIS as 'a real-time, label-free, impedance-based method to study the activities of cells grown in tissue culture' (Giaever & Keese 1984, 1986). At the time, having just returned to academia, he was in need of graduate students. I rotated through various labs but finally ended up in his lab, as his first PhD student.

It was Dr Keese who taught me tissue culture and the rudimentary biology I should have learned in my

undergraduate years. I took all the core courses that the Chemistry Department required of me, but filled up my schedule with any biology, biochemistry or molecular biology courses I could find. In Dr Giaever's lab, I learned how to vacuum-deposit gold electrodes on the bottom of standard polystyrene culture dishes and coat them with various proteins. I used that technology to measure the attachment and spreading of cells in tissue culture and to compare the results with those obtained by time lapse microscopy. I showed that, as cells attach and spread on the electrodes, the impedance of the electrodes change, which reflect the area blocked by the spreading cells. In 1991, shortly after my wedding to a fellow RPI student, I published my first paper under my maiden name (Mitra *et al.* 1991).

I published two other papers in that lab. I used ECIS technology to develop a novel method of electroporation, whereby the effect of electroporation on the same cells could also be monitored by the ECIS electrodes (Ghosh *et al.* 1993), and also developed technology to see what happens when AC pulses are used instead of DC (Ghosh *et al.* 1994). These papers formed the basis of my PhD thesis, which I completed in 1994. I also received and accepted an offer to work as a postdoctoral fellow in San Antonio, TX in Dr Robert Klebe's group.

### Learning biochemistry (or maybe molecular biology)

Dr Klebe's lab was committed to technology development. At the time I joined the group, they were in the process of developing computer-controlled micropositioning of both mammalian cells (using a computer-controlled X-Y translation table and a fluorescence-activated cell sorter (FACS)) and cell adhesion proteins (using an inkjet printer) (Klebe *et al.* 1994) (my name is misspelled as 'Gosh' in that paper). A second project that I participated in studied the 3-dimensional growth of an epithelial cell line. We observed organogenesis on a dish, which was obvious from the tubular structures with lumens that the cells produced when grown at very high densities (Klebe *et al.* 1995). This was my first introduction to signal transduction. We learned to differentiate between responses using protein kinase A (PKA) and protein kinase C (PKC) modulators. To a could-have-been physicist, the concept that proteins, and not mechanical forces, can be used to regulate a biological structure was an eye opener (Klebe *et al.* 1995).

Shortly after, my husband and I discovered that I was pregnant. The first pregnancy is always scary, and Dr Klebe's lab housed many chemicals that were labeled teratogens. I left the lab, but after she was born I helped finish a manuscript in progress. When she was on bottled milk and old enough to go to day care, I ventured back to a lab job. This time, I wanted to learn *how* proteins control structure. I found another lab, directed by Dr Jeffrey Kreisberg, where the same pathways, regulating PKA and PKC, were being studied.

Dr Jeffrey Kreisberg was an experimental pathologist in the Department of Pathology in the University of Texas Health Science Center at San Antonio (UTHSCSA). His area of study was the investigation of PKA and PKC pathways in glomerular mesangial cells. Dr Kreisberg had perfected a technique to isolate these cells from rat kidneys, and he was now studying the pathways in isolated cells. I learned a lot about PKA and the various PKCs and their influence on the structure of the glomerular mesangium from Dr Kreisberg, but my first paper in that lab was to determine the effect of lovastatin on glomerular mesangial cells and how it regulated small GTP-binding proteins of the Rho family (Ghosh *et al.* 1997).

My introduction to the small GTPase RhoA turned out to be fruitful. We would continue to study various signal transduction pathways that regulated glomerular mesangial cells, most notably the epidermal growth factor receptor (EGFR) pathway (Ghosh *et al.* 2001) and the ERK and Akt/mTOR pathways (Ghosh *et al.* 2004). We also showed that lovastatin and RhoA regulated cell cycle progression in NIH3T3 cells (Ghosh *et al.* 1999b). By that time, based on my results on the effects of lovastatin and RhoA on cell proliferation, Dr Kreisberg had already decided to see if these proteins regulated growth and apoptosis in tumor cells.

### A disease called prostate cancer

Dr Dean Troyer was an Anatomical and Clinical Pathologist whose office was right next to that of my mentor Dr Kreisberg. When he heard that we were looking for a disease to cure, he offered his insight in prostate cancer (CaP). Dr Troyer provided me with three cell lines called LNCaP, PC-3 and DU-145. 'What are these?' I asked. Dr Troyer was very patient: 'They are prostate cancer cell lines', he explained. I was puzzled. 'What is a prostate?' I asked. (Since then, I have become savvier. Now that the internet is so widely available, and responses to all sorts of questions can be obtained there, I submit questions to the internet before I ask a human being.)

Dr Troyer's tutorial was the pivot that I needed to redirect my research interest. We showed that the same agents that I had been studying in glomerular mesangial cells, lovastatin and RhoA, also had significant effects in CaP cell lines (Ghosh *et al.* 1999a). We would later follow this up with another study that showed that the effects of RhoA were dependent on Akt and p70S6 kinase phosphorylation via a mechanism that involved PKC $\zeta$  (Ghosh *et al.* 2004).

Around that time, Dr Nandini Ghosh-Choudhury joined Dr Kreisberg's lab. I think I learned more about signal transduction pathways talking to her and her husband Dr Goutam Ghosh-Choudhury who was (and is) knowledgeable in all things related to molecular biology. They knew not only what pathways were important but also how to study them. Nandini was in Dr Kreisberg's lab for a very short time, and we have only one paper together (Ghosh-Choudhury *et al.* 2000), but the many things I learned from her would always stay with me.

### Science with tissues, animals, genes

Around this time, Dr Michael Brattain came to town with his group of about 30 people. When Dr Brattain, Dr Jim Freeman, Dr Luzhe Sun and Dr Gokul Das had settled down in the Department of Surgery, Dr Kreisberg and his lab moved from pathology to surgery to join them. By that time, I had been a postdoctoral fellow for 4 years, and now I received a new title – 'Research Assistant Professor'. This meant that I could write grants and pursue my own interests. I promptly wrote a small grant and received funding. Being part of the Molecular Oncology Group in the Department of Surgery was educational. We had journal clubs together, and participated in group meetings. I learned new pathways every week and how those pathways worked. We wrote papers together on topics of common interest (Sawhney *et al.* 2002), and in general learned how to work closely as a team. When Dr Brattain and his group left the university, and Drs Freeman and Sun moved to other Departments, the energy dissipated and the once active labs felt empty and stagnant.

In the meantime, soon after my son was born in 2001, I started working more closely with the Department of Veterans Affairs (VA). Dr Kreisberg had always been funded by the VA, but his lab was in the university. His friend Dr Michael Katz on the other hand was a geriatrician who had a lab inside the VA hospital. Dr Katz worked on a rat model of liver aging and needed my help to conduct a few experiments. At first I was not sure I would be able to do it, but after killing the first rat, handling small mammals

became easier. The data I collected from that project was utilized in publications later (Kamat *et al.* 2008, Ghosh *et al.* 2012). While working with Dr Katz, I collaborated with a dentist, who also had a lab inside the VA. Here I utilized my newly acquired knowledge of the EGFR pathway to help him determine how they regulate the salivary gland (Yeh *et al.* 2005). I learned a lot about PKA and cAMP-related pathways, and G-protein coupled receptors (GPCR) during that project, which I would be able to utilize years later in other contexts (Vinall *et al.* 2011). More importantly, I established a relationship with the VA. My first large grant, after the small award, was an internal VA award. I maintained relations with Dr Katz's group even after these projects were completed.

Shortly before Dr Kreisberg's lab left Pathology, we had two new recruits: a pathology fellow, Dr Shazli Malik, and Dr Roble Bedolla, a physician scientist from Mexico who chose not to do a residency in the United States. For the first time in my life, I realized the power of research in human tissues. Dr Malik, working with Dr Troyer, collected archived prostatectomy samples, and Roble showed me immunohistochemistry techniques for protein detection in human tissues. Our most highly cited publications resulted from this period, and showed the role of Akt and ERK phosphorylation in CaP progression (Malik *et al.* 2002, Kreisberg *et al.* 2004). Roble and I continued to work together even after Dr Kreisberg retired and I moved (Bedolla *et al.* 2007).

## Cancer biology

In 2004, my husband's job moved from San Antonio, TX to San Jose, CA, USA. At almost the same time, Dr Kreisberg announced his imminent retirement. I quickly realized that I had to move too. Fortunately, I had received an exploration grant from the National Institutes of Health (NIH), and a VA Merit Award, both almost simultaneously. I sent my resume to universities initially closest to San Jose, and then further away. The UC Davis School of Medicine in Sacramento was only about a hundred miles from San Jose, and I applied there. One day the phone rang. It was Dr Ralph W deVere White, the Director of the UC Davis Cancer Center. I had sent him my resume, and he wanted to know if I could go to Sacramento for an interview. Dr deVere White was at the time also the Chair of Urology, and I was recruited into the Department of Urology as an Assistant Professor in 2005. Space was limited in the UC Davis labs in Sacramento, so I was provided lab space at the VA in Mather. Finally, I was on my own!

Setting up a new lab is always exciting. In this case, what made it even more interesting was that the VA labs were almost completely empty. The few researchers there included Dr John Peters, a geriatrician who studied osteoarthritis, and his technician Sam Vaughn; Dr Andrew Vaughan, a radiation biologist who studied genetic instability in irradiated patient tissue, and his research faculty Dr Grace Loreda, and Dr Joanna Albala, who was also a radiation biologist who had come to the VA from Lawrence Livermore National Lab one month before me. I hired a technician, Helen Lu, and very soon, Yu (Colin) Wang joined me from San Antonio. Colin had been Dr Kreisberg's graduate student, but when Dr Kreisberg retired, I inherited Colin. In San Antonio, Colin had helped me with a publication comparing the effects of the androgen receptor (AR) to that of the PI3K/Akt/mTOR pathway in CaP cells (Ghosh *et al.*, 2005), and I was very pleased with his efforts. Therefore, I happily brought him into the fold and tasked him with various projects.

Dr George Kaysen, a nephrologist, was affiliated to the VA and was the acting Chair of the Department of Biochemistry and Molecular Medicine. He saw my resume and asked if I wanted a joint appointment with his department. My affiliation with biochemistry introduced me to Dr Hsing-Jien Kung, who is the most patient mentor any new faculty member could have asked for. Between collaborations with Dr Kung and Dr deVere White, my lab learned a lot about the AR. We published together on AR mutants (Shi *et al.* 2007), and on a natural product called Genistein Combined Polysaccharide (GCP) (Vinall *et al.* 2007).

In the meantime, Colin from my lab was studying the effect of the actin-binding protein Filamin A. Colin discovered that Filamin A cleaves into a smaller fragment and moves to the nucleus in androgen-dependent and not in-castration resistant CaP (CRPC) (Wang *et al.* 2007). Later, Roble, with whom I was still collaborating, found that tissues from normal prostate show the cleaved form of Filamin A in the nucleus while those from patients with CRPC do not (Bedolla *et al.* 2009). Eventually, another student, Ben Mooso, would show that the effects of GCP on CaP are mediated by Filamin A cleavage and nuclear localization (Mooso *et al.* 2012).

Colin also showed a synergistic effect of the combination of the anti-androgen bicalutamide, and the mTOR inhibitor rapamycin in CaP cell lines (Wang *et al.* 2008). The basic premise was that in non-tumor prostate, the mTOR pathway promotes AR transcriptional activity, whereas in castration-resistant tissue, mTOR has the opposite effect. In support of this observation, Dr Karim Chamie,



then a urology resident at UC Davis completing his research rotation, showed that in renal transplant patients treatment with the immunosuppressant rapamycin reduced PSA levels (Chamie *et al.* 2008). A medical oncologist in the Cancer Center and the VA, Dr Chongxian Pan, would later use these results to design a Phase II trial to test the efficacy of bicalutamide and rapamycin in CaP patients (Chow *et al.* 2016), and show that about 75% of the hormone refractory patients responded to this combination. This work led to my first large NIH award, and work on this topic continues to this day.

## Still learning

I had always been interested in the EGFR family. I collaborated with Dr Imran Khan of the Proteomic Core Lab in the Pathology Department to develop new technology for the detection of this family (Khan *et al.* 2010). Other collaborations with Dr Andrew Vaughan at the VA had also yielded publication (Mooso *et al.* 2010). One collaboration that has lasted a very long time is with Dr Maria Mudryj, a geneticist in the Department of Medical Microbiology and Immunology who studied CaP progression. Dr Mudryj showed that the AR can be post-translationally modified by calpain cleavage in CaP (Chen *et al.* 2010b) by a mechanism involving ERK phosphorylation. With her tutelage, I had learned how to analyze genome-wide analyses of large-scale datasets (Chen *et al.* 2010a). I still collaborate with Dr Mudryj, even as she refocuses her efforts to study the effects of miRNA in bladder cancer (Lombard *et al.* 2016).

Another collaboration that has persisted over time is with Dr Ruth Vinall. When I first came to UC Davis, Ruth was a member of Dr deVere White's lab. Since then, she had moved to *her* first independent position in the California Northstate School of Pharmacy, but we still continued to collaborate, recently publishing a paper together on the effects of microRNAs in bladder cancer (Vinall *et al.* 2016). Collaboration with Dr Pan, the medical oncologist who had conducted a clinical trial based on my 2008 study also yielded a publication on the utility of patient-derived xenografts (PDX) on individualized therapy in bladder cancer patients (Pan *et al.* 2015). These collaborations all taught me something new, something important, and something I would not have otherwise learned.

The most important lesson that I have learned is that you never stop learning, and that your teacher could be anybody whom you come in contact with – especially your students. Liqun Chen was my second graduate

student, after Colin. I tasked her with deciphering the mechanism by which ErbB3 works in CaP cells. One day she attended a seminar at the cancer center and came back to the lab very excited. The seminar was from Dr Kermit L Carraway, III, in the Department of Biochemistry and Molecular Medicine, who had identified an E3 ubiquitin ligase Nrdp1 as a negative regulator of ErbB3 in breast cancer cells. She was adamant that this novel protein was the mechanism that she had been looking for. Initially I tried to dissuade her. That work was done in breast cancer, I explained.

But Liqun persisted. Yielding to that irrational demand (or so I thought at the time) was one of the most fruitful decisions I have ever made. Liqun went on to show, with the help of other members of Dr Carraway's lab, that Nrdp1 was a transcriptional target of the AR, and that the androgen axis suppressed hormone-independent cell growth in hormone-naïve cells by inhibiting the EGFR–ErbB3 pathway through manipulation of Nrdp1 expression (Chen *et al.* 2010c). In 2011, Liqun showed that in castration-resistant cells, the AR fails to suppress the EGFR–ErbB3 axis, causing sharp increases in their activity, which could however be inhibited by a combination of an EGFR and an ErbB2 inhibitor (which resulted in ErbB3 inhibition as well) (Chen *et al.* 2011). The third student, Rosalinda Savoy, would continue that work and show that the ability of the AR to regulate Nrdp1 depended on the availability of cleaved Filamin A (Savoy *et al.* 2015). None of this would have been possible without Liqun's initial insistence.

Many other developments have taken place since Liqun has graduated. New students – Leandro D'Abbronzo, Maitreyee Jathal and Sophie Kiss – now are bringing new ideas to the lab that I am heartily approving and absorbing. We are starting new collaborations with other faculty and other institutions. And through it all, I continue to learn.

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The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this profile. The work reported here does not represent the views or opinions of the Department of Veteran Affairs or the United States Government.

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