

# JOINING THE FIGHT AGAINST CANCER

## My Internship at the NIH

by Roy Ghosh

Ever since I participated in my first laboratory internship in middle school, I imagined someday being a researcher at the National Institutes of Health (NIH), the largest biomedical research center in the world, as the culmination of a career. To me, the Bethesda campus—replete with barbershops, grocery stores, and gyms, as well as 27 medical facilities—seemed like a commune of medical progress where I hoped to spend my adult life. Last year, when I went online to see if I could tour the campus, I learned that I could do more than just visit. I might be able to work there.

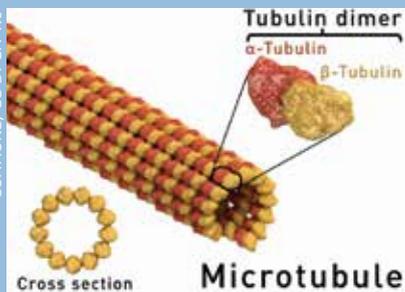
### A Foot in the Door

In applying for the Summer Internship Program, I emailed one of the researchers whose name was familiar to me from papers I had read while interning at a Lehigh University lab that was studying metastatic

cancer: Dr. Dan Sackett of the National Cancer Institute and Institute of Child Health and Human Development. As I read about Dr. Sackett's work on cellular structures called microtubules and their relationship to cancer, I realized that it was similar enough to my work at Lehigh that I would be able to understand it, yet different enough that I would find it engaging. My email message led to the best possible outcome for a young researcher: He offered me an internship position in his lab, starting in mid-June.

I struggled to keep my cool as I walked onto the 200-acre campus on my first day. It was surreal as I flashed my badge at the security guards on my way to work with a world-renowned biophysicist. As it dawned on me that I was there to contribute to life-saving work, I became even more excited about the experience that lay ahead.

USER:SPLETTE, WIKIMEDIA COMMONS, CC BY-SA 4.0



**Above:** Microtubules are filamentous structures composed of dimers of alpha and beta tubulin. Part of the cell's cytoskeleton, microtubules are also involved in many cellular processes, including mitosis, during which they pull apart the cell's chromosomes.

**Right:** In this cell undergoing mitosis, the chromosomes (purple) have already replicated and the duplicates are being pulled apart by microtubules (green). Some chemotherapeutic drugs work by targeting tubulin to prevent cell division.



NASSER RUSAN, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE, NIH

### Finding My Focus

For the next 10 weeks, I spent nearly every day on the NIH campus. During my first week, Dr. Sackett suggested that we design some research based on his previous work with microtubules.

Dr. Sackett was interested in a drug called colchicine, which is commonly used to treat a form of arthritis called gout. Colchicine works by depolymerizing, or breaking down, microtubules, thereby disrupting mitosis. Colchicine has recently been shown to have curative effects in a variety of unrelated illnesses: ischemic heart disease, prostate cancer, and a connective-tissue disorder called epidermolysis bullosa. Surprisingly, when low doses of colchicine were given to patients, no normal cells were affected, but all diseased cells underwent mitotic arrest and death, even though depolymerization should have affected all cells.

ISTOCK.COM/VOYAGER624

Finding no explanation in the scientific literature for why this would be the case, Dr. Sackett and I came up with a research plan to determine how colchicine and some other anti-microtubule chemotherapeutic drugs interact with different structures in cells. We would do this by measuring the drugs' effects on specific proteins in the cell.

### **Dramatic Discoveries**

We knew from prior research that some proteins had a huge increase in expression after drug treatment, meaning that they were upregulated by the drug. For example, one component of microtubules called beta-tubulin has been found to increase two- to threefold after colchicine treatment. We predicted that this increase might explain colchicine's unique effects in treating disease.

The initial step in our research was to map the expression of 200 genes, including the 18 that code for the different proteins found in microtubules, in both normal and cancerous cells, both before and after exposure to chemotherapeutic drugs. Analysis of the expression map revealed much more than we expected. For example, several papers on the composition of microtubules in platelets relied on data from nearly 30 years ago. Techniques for measuring protein expression have advanced significantly since then, so we repeated the testing using modern instruments. Upon retesting, we found that the protein made up only 30-35% of the microtubules instead of 90%, as the previous studies had shown. We also found that one drug that was thought to work by upregulating one protein was also downregulating another protein in a different part of the cell.

Each surprising result led to another line of inquiry, and our research soon developed into several related but different lines of investigation. Inadvertently, we ultimately identified novel markers that could be targeted by a combination of chemotherapeutic drugs in the case of metastatic cancers. Further, as we measured protein differences between cancerous and non-cancerous cells, we noticed an upregulation of certain proteins in the cancerous cells. We hypothesized that there would be further upregulation of those proteins during metastasis. To our surprise, our method of measuring this protein (which also measures depolymerization rate) turned out to be an effective diagnostic procedure: The calculated rate of depolymerization and amount of protein expression could actually track the progress of cancer and diagnose the stages of cancer during metastasis. Without initially setting out to do so, we had developed the first non-toxic procedure to measure and diagnose not only primary cancer, but also progression and metastasis.

The final finding of these projects was a valid, testable explanation of why many chemotherapeutic drugs do not work, no matter how high a dose is administered. By measuring protein expression in cells exhibiting multidrug resistance (MDR), we identified the specific genes responsible—meaning we had found genes that can be targeted in order to make tumors susceptible to drugs again.

We could not have predicted the depth of this project at the beginning of the summer, but from an initial goal of just trying to understand



colchicine's actions, we ended up completing a five-part investigation into the protein tubulin and its various isotypes, as well as colchicine's effects on heart disease, prostate cancer, and epidermolysis bullosa.

### **The Ideal Environment**

This revolutionary research could not have been possible without the facilities and opportunities available at NIH. For instance, when analyzing microtubules' three-dimensional structure, I worked with a scientist at the National Cancer Institute who was developing his own scanning electron microscope. This new device provided a complete map of the microtubule, including the C-terminus, the moving tail portion rarely seen in images.

I also had the opportunity to meet hundreds of scientists every week during lab meetings and department presentations. The 13 researchers in Dr. Sackett's group met weekly to discuss the progress of projects and validate proposals or arguments, and my thoughts were valued as part of the discussion, which gave me a new confidence in my work.

When my internship ended, Dr. Sackett and I planned the next few months of communication to continue our research and begin drafting the five papers we plan to submit for publication. I remain grateful for the incredible experience I've already had. My internship did more than just satiate a teenage fascination with a leading research organization. My work with Dr. Sackett showed me that I can contribute to research with the potential to cure diseases in the real world, and not just in my imagination. ■



**Roy Ghosh** is a junior at Parkland High School in Allentown, PA, where he founded his school's nationally ranked Science Olympiad team. An International BioGENEius finalist, ISEF Second Award winner, and Science Olympiad national medalist, Roy has been an invited presenter at meetings of three national scientific organizations. In his free time, he plays piano, scuba dives, and loves to travel around the world.

**Learn more about the NIH Summer Internship Program at [training.nih.gov/programs/sip](http://training.nih.gov/programs/sip).**