My amazing ‘URP’ summer

The author (third from left) and 26 fellow URPs, class of ‘13

by Alexis Tchaconas
Columbia University Class of 2014

When I first arrived at Cold Spring Harbor Laboratory in early June, I knew this wouldn’t be a typical summer. Even though I had worked in labs over past summers, never before had I completely immersed myself in science as I did during my 10 weeks as an “URP,” a participant in the Undergraduate Research Program.

I was pleasantly surprised when I arrived and noticed all of the conspicuous artistic references to DNA throughout the campus, planted for the appreciation of biology lovers like myself. On our first tour of the grounds I marveled at the “Waltz of the Polypeptides,” an arresting steel sculpture that unfurls itself across the hillside beside the Dolan building; and Beckman Lab’s rectangular clock tower, each of its four sides adorned with one of the letters representing the DNA bases (A, T, C, G). As someone fascinated by genetics, I felt immediately at home in seeing these and other campus tributes to DNA.

Unlike most URPs, who are assigned to their faculty mentor after applying, I chose to reach out directly, to Dr. Michael Wigler, before applying. The Wigler lab uses quantitative biology to investigate the mechanisms of genetic disorders like autism—an approach I wanted to learn more about. My interest was fueled by my personal connection to the disorder, as my older brother has autism.

I had just spent my junior year in college studying at the University of Oxford in the U.K., to better integrate my neuroscience major at Columbia University with my linguistics concentration. I have a great love of language and have come to appreciate its importance in science and medicine. But I also know that it is one of the things most commonly affected in autism, a disorder whose symptoms affect various aspects of social interaction. At Oxford I had the opportunity to conduct research on language impairment in Dr. Dianne Newbury’s lab, where I was fascinated to learn that quantitative biology programs can scan sequencing data from an entire genome and find potential disease-causing mutations within minutes!

From that point on, I knew that I wanted my next research experience to be in quantitative biology—which is why I got in touch with Dr. Wigler. I remember our first interaction via e-mail; he responded within 5 minutes, encouraging me to submit an application for the URP program under his tutelage.

On my first day as an URP, Dr. Wigler was eager to welcome me as a member of his lab. After updating me on the lab’s current work, he and I brainstormed project ideas that could be tackled during my 10 weeks at CSHL. Given that most genetic studies on autism have focused their analyses on DNA contained in the nucleus of cells—this is called nDNA, for nuclear DNA—we thought it would be worthwhile investigating another source of DNA, existing in the cell’s plentiful energy-producing compartments called mitochondria.

DNA in mitochondria (mtDNA) is interesting in that it has a 5 to 15 times greater mutation rate compared to DNA found in the chromosomes. There would be plenty of material to study since multiple copies of mtDNA exist in each mitochondrion, and thousands of mitochondria can exist in a single cell.

The mitochondria, seen in this way, are a relatively understudied “hotspot” for genetic mutation. Autism is a neurodevelopmental disorder and mitochondria are highly expressed in nervous tissue, so mutations in mtDNA could alter energy production and thereby affect proper brain functioning. Furthermore, autism has a male bias—it affects far more males than females—and it so happens that males tend to have more mtDNA mutations than females.

URPs of yesteryear: (top) Alan Rein (‘61) with Dr. A. Chovnick; (bottom) David Baltimore (‘59) with Dr. B. Kaufmann

Dr. Wigler and I designed a study to analyze mtDNA sequencing data from families whose DNA is sampled in the Simons Simplex Collection (SSC). These “simplex” families are ones with two or more children, only one of whom is diagnosed with autism. (This is in contrast to “multiplex” families, with more than one autistic child.) The objective of my project was to ascertain how often children with autism inherit mtDNA that is significantly different from their mothers’ mtDNA, or inherit mtDNA in altered proportions.

After completing 10 weeks of URP research, I had made much progress in answering my research question—so much that I continued my project in the Wigler lab until I had to return to Columbia in late August. I can now offer this progress report: we have identified a bias for the emergence of new mtDNA mutations in children with autism, relative to their normal siblings. I am working on characterizing these mutations and analyzing more simplex families in additional data we’ve received from the SSC. The hope is that such work, beyond autism, could more broadly elucidate the biological mechanism of mitochondrial inheritance and its role in disease.

I will keep in contact with Dr. Wigler, as he has served as a nurturing mentor and an inspiring role model. And I will always have warm thoughts about CSHL and the URP program as a whole, which, outside of my research project, helped me learn more about what it means to be a scientist outside the lab and how to thrive in a scientific community.

An historic incubator of young talent

Each year since 1959, CSHL’s Undergraduate Research Program (URP) has offered up to 25 American and foreign undergraduate students a priceless opportunity to study side by side with some of the world’s most distinguished scientists. The fully subsidized, 10-week summer program offers independent research projects in Cancer Biology, Neuroscience, Plant Biology, Cellular and Molecular Biology, Genetics, Bioinformatics and Genomics. A few of the notable alumni include Dr. Gerry Rubin (HHMI, Janelia Farm Research Campus), Dr. Alfred Goldberg (Harvard Medical School), Dr. Geraldine Seydoux (Johns Hopkins), Dr. Charles Gilbert (Rockefeller University), and Nobel laureate Dr. David Baltimore (California Institute of Technology).

Administered by the Watson School of Biological Sciences (WSBS), the URP course is designed to give students the skills and opportunity to conduct first-rate research. Applications are submitted online, and the deadline for the Summer 2014 program is January 15, 2014. For further information about the program, visit the webpage: cshl.edu/education/urp or send an email to urpadmin@cshl.edu.

Who gets to be an URP? Alexis' backstory

I grew up in East Northport, Long Island, and went to Commack High School, where I took advantage of the prestigious International Baccalaureate program and the school's phenomenal science research department. It was there that I got my first exposure to research and was encouraged to participate in nearby Stony Brook University's (SBU) biotechnology program the summer before my junior year. There I learned advanced biological laboratory techniques like polymerase chain reaction, or PCR, in which you can greatly amplify tiny samples of DNA; and plasmid preparations, a way of purifying bacterial DNA.

Armed with these techniques, I returned for my junior year in high school and planned an investigation to explore a candidate gene that had been recently associated with autism: *contactin 4* (CNTN4). It is thought that having certain "risk" genes makes a person more susceptible to developing the illness. I began by searching public gene databases, where I found a version of this human gene in the roundworm, a simple model organism called *C. elegans*.

The summer before my senior year in high school, I was able to arrange with Dr. Lorna Role, chair of SBU's neurobiology department, to continue with this research in her lab as a Simons Foundation Summer Research Fellow. For this work I was named an Intel Science Talent Search semi-finalist, a New York State & Long Island Science Fair First-Place Winner, an Intel International Science & Engineering Fair (ISEF) Finalist, and a National Junior Science & Humanities Symposium (NJSHS) Finalist.

The following fall I entered Columbia University, where, during my first semester, I began researching in Dr. Martin Chalfie's neurobiology lab. I had already been lucky enough to have worked in my junior year in high school under the direction of Dr. Andrew Adesman, a developmental-behavioral pediatrician, with whom I co-authored a review article in *Current Opinion in Pediatrics*. Working with Dr. Chalfie on the clinical side of autism research confirmed my interest in a career as a physician-scientist.

It was at this point that I was accepted at the University of Oxford for my junior year of college—the experience that led me to write Dr. Wigler and apply for the URP program.

Once I graduate from Columbia this coming spring, I hope to pursue a 1-year research master's degree in the U.K. Ultimately, I hope to have both an M.D. and Ph.D., because I want to directly translate my findings at the bench to clinical applications at the bedside. It's the next step in what has already been an amazing journey, enabling me to merge a personal connection to autism and an intellectual interest in genetics into a lifelong effort to improve treatment, detection, and prognosis of people with autism.

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