BIOTECH SCHOOL’S IN FOR SUMMER

Who do you call when a new research technique debuts on the scientific stage and you want to learn it fast?

Hundreds of scientists, with backgrounds in academia and industry, have turned to the UC Davis Biotechnology Program.

Since 1988, the Biotechnology Program has offered two- to five-day intensive courses, open to the public, that combine lectures with laboratories designed to give participants hands-on experience with a particular research technique.

Martina McGloughlin, director of the Biotechnology Program, is aware of only a few other places in the United States where people can take classes similar to the ones her program offers.

The courses change to keep pace with and reflect developments in biotechnology.

Says McGloughlin, “In 1989 the Biotechnology Program offered its first intensive summer short course. It was a course in DNA manipulation, and we offered it because many people had gone through school before these new techniques were taught. We had mostly faculty in the first classes—biochemists and physiologists who were trying to catch up on the new technology.”

McGloughlin realized the initial DNA manipulation course targeted a finite audience since the techniques would now be part of a student’s education. Therefore, in 1990, the program offered a DNA sequencing class. “When we offered the class, people didn’t have automatic DNA sequencers,” says McGloughlin.

Once automatic sequencers supplanted the do-it-yourself method the sequencing class became obsolete.

McGloughlin mentions another example...
Research News

Watch DNA Unzip in Micromovie

By Carl T. Hall

Using some extraordinary camera tricks, scientists at the University of California at Davis have produced Lilliputian action shots of molecular “motors” unwinding strands of DNA.

Close to four years in the making, the grainy black-and-white movie stars an enzyme called helicase, chugging along brightly lit tracks of fluorescent-dyed microbial DNA.

The footage lasts only about a minute, but it’s already attracting attention from other researchers who are trying to peer into the excruciatingly tiny realm of molecular motion.

“I have seen the movie,” said Ron Vale, a biochemist at UC San Francisco. “It’s striking, and it’s completely clear... It’s really amazing that you can now see single protein molecules in motion doing their work.”

The images underscore recent dramatic advances in the field of nanotechnology, a discipline that scientists hope will allow various inheritable diseases, sensitivity to sunlight and certain forms of cancer.

It has been difficult to figure out how the enzymes go about their routine business in a molecular world too small to be glimpsed directly. Now, Kowalczykowski and his colleagues are hoping to harness the process for medical purposes, including gene therapy and ultra-precise delivery of DNA-repairing drug payloads.

“Our very simple goal was to see in real time a molecular motor running along a strand of DNA, something that has never been visualized before,” Kowalczykowski said.

It took a combination of sophisticated tools and custom engineering to make the DNA stretch out sufficiently and hold still long enough to be photographed while the enzyme molecules were attached.

Lighting was provided by special fluorescent dyes that make DNA glow when it is in its typical double-stranded form, but not when the molecule has been unzipped into two single strands.

Glowing polystyrene beads were attached to one end of each piece of DNA to help anchor them down. The researchers also wielded laser beams as pairs of high-precision “optical tweezers” to help keep things under control.

A single helicase molecule, attached to a DNA molecule, was then loaded into one channel of a Y-shaped micromachined “flow cell.” The action began when the ATP was added as fuel through the other arm of the “Y.”

At that point, the video camera began recording the scene through an optical microscope, capturing the glowing DNA as the enzyme molecules marched along toward the polystyrene anchors.

The enzyme molecules are too small to be seen one at a time, even under the...
microscope. And technical problems made it impossible to use more advanced nanotech imaging methods that make pictures by recording subtle atomic forces.

So the researchers had to settle for the indirect strategy of the special dye. As the enzyme unzipped the DNA into its two separate strands, the light appears to blink out in the enzyme’s wake. The pictures show the DNA strands seemingly growing shorter and shorter.

In the end, only the polystyrene bead is still visible, even though the unlit DNA still dangles in place.

Kowalczykowski said additional experiments are planned to better understand how the enzymes work at the level of individual molecules—activity that biochemists traditionally have studied by mixing test tubes and beakers containing molecules by the millions.

Looking at a single molecule as it changes form is “a very powerful approach,” Kowalczykowski said. “If you want to know how a car works, you can take an aerial view of Interstate 80 and see thousands of cars at once, which can tell you something,” he said. “But if you really want to understand how a car works, eventually you have to take a close look at a single car.”

**FIRST FLOWERING PLANT GENOME SEQUENCED**

The first complete genome sequence for a flowering plant, Arabidopsis thaliana, was published on Dec. 14 in the journal Nature. Anne Britt, professor in the Section of Plant Biology, contributed to the report.

Arabidopsis is a small, fast-growing plant widely used in plant biology research. The completed genome sequence may open up ways to study human diseases using plants.

The researchers found unexpected similarities to, and differences from, other organisms that have been sequenced, such as the yeast Saccharomyces cerevisiae, the fruitfly Drosophila, and the soil roundworm Caenorhabditis elegans.

Teams of scientists examined the DNA sequence for genes with particular functions. Britt, in collaboration with Jonathan Eisen of The Institute for Genome Research, looked for genes that repair damaged DNA.

“Twenty-seven genes were identified in Arabidopsis that were closely related to human disease genes,” said Britt. Of these, a third were DNA repair genes, including genes linked to some types of breast and colon cancer, and to the hereditary disease xeroderma pigmentosa, which makes children extremely susceptible to skin cancer.

“Arabidopsis has a similar distribution of repair genes to humans. Arabidopsis might turn out to be a very good model for the study of DNA repair in mammals,” said Britt.

UC Davis has established a national presence in the study of DNA repair and chromosome biology, according to Stephen Kowalczykowski, director of the Center for Genetics and Development.

**MICROBIOLOGISTS PLUMB THE DEPTHS**

A remote-controlled submarine is being used to study mysterious bacteria living half a mile below the surface of Monterey Bay. UC Davis microbial ecologist Doug Nelson, professor in the Section of Microbiology, leads the research.

The team uses a remote operated vehicle (ROV) owned and operated by the Monterey Bay Aquarium Research Institute (MBARI). The ROV Ventana is equipped with high-definition cameras and laser measuring equipment, and its arms can be fitted with a variety of collecting and sampling equipment.

Because of their strange and hostile habitat, deep-sea bacteria have evolved survival strategies found nowhere else on Earth. Far from the sun, they live on hydrogen sulfide seeping from cracks in the seafloor and use nitrate in seawater instead of oxygen.

One example is Thiomargarita namibiensis, giant bacteria that grows to almost a millimeter in size—100 times the size of any other known bacterium. Thiomargarita was discovered in 1999 in deep water off the coast of Namibia in southern Africa, by a team led by German scientist Heide Schulz.

This year, Schulz will join the UC Davis researchers studying bacteria around sulfide seeps in Monterey Canyon. Nelson’s lab is particularly interested in Beggiatoa, bacteria that grow in long filaments on the seafloor mud.

Although these bacteria are deep in the ocean, they can be affected by fertilizer runoff, aquaculture and dumping of waste at sea, said Nelson.

“If you insult the ocean in a significant way, it will result in a die-off,” said Nelson. That could lead to a release of hydrogen sulfide from the seafloor, which could affect fish and other marine animals and plants.

Website: http://www.mbari.org/dmo/ventana/ventana.html.
Botany Professor Emeritus John Tucker says he hopes his $500,000 gift will help ensure a financially secure future for the herbarium and arboretum. "I’ve been interested in these two facilities my entire career," he says.
oaks and to fund educational and interpretive programs relating to the Shields Oak Grove.

“Dr. Tucker’s gift is especially meaningful because of his role in developing our outstanding oak collection and because of his strong leadership as arboretum director in the 1970s and 1980s.”

An authority on oak hybrids, Tucker said he developed a fascination for the stately trees while participating in scouting activities as a teenager in Santa Barbara in the 1930s.

With little money during the Depression for other activities, his scoutmaster took him and other members of his Boy Scout troop on weekend hikes and camping trips where they learned to identify the local trees and shrubs.

About the same time, the local natural history museum had an exhibition on oaks native to Santa Barbara County. “I was amazed to see how many different kinds there were. So I went back repeatedly.”

Tucker said he pestered the curator into telling him where the different varieties grew. “It wasn’t too long before I found myself hitchhiking to places where I could see these oaks.”

On his longest trip, when he was about 16, he hitchhiked nearly 120 miles to the foothills of the San Gabriel Mountains in northern Los Angeles County to see the southernmost grove of Oregon oak. A forester who drove him the last leg of the trip in his pickup truck became a lifelong friend.

Tucker was the third of eight children born to a farming family in the tiny western Oregon community of Amity. His family moved to Ithaca, N.Y., when he was a toddler, then settled in Santa Barbara when he was four.

After graduating from high school in 1934, he enrolled at what was then Santa Barbara State College (now UC Santa Barbara). He transferred as a junior to UC Berkeley where he graduated with honors in 1940.

He entered graduate school at UC Berkeley, where he studied under the likes of G. Ledyard Stebbins, a pioneering plant evolutionist who would join UC Davis not long after Tucker.

World War II interrupted Tucker’s doctoral studies. With poor eyesight keeping him from enlisting, he went to work as a machine welder for a Naval shipyard in Richmond. Later, he worked for a Shell Oil research plant in Emeryville as an overnight lab monitor, checking on chemists’ experiments, until his major professor persuaded him to return to graduate school. He did even though it meant sacrificing his $200 monthly salary to earn $95 a month as a teaching assistant.

He and his wife, June, a fellow UC Berkeley graduate and the only child of a bank vice president, moved to Davis in 1947 while June was expecting the first of their three children.

Tucker joined the faculty of what was then the Botany Department and is now the Section of Plant Biology.

His research focused on taxonomy of oaks and intermingling of oak species. “Oaks have a long reputation of being a difficult group to classify taxonomically. They’re horrendously variable, so it’s hard to draw a line from where species A starts off and species B begins.”

Tucker shares an office near the herbarium and still conducts research. However, he said he no longer approaches it with the same single-minded intensity as he did before his wife died of cancer in 1987.

Other interests also occupy his time, he said. A self-described newspaper addict, he reads three newspapers daily as well as a number of other publications. He also has traveled to China, Central America, Scandinavia and Russia since retiring.

“There’s no question I’m slowing down. The desire is still there but my research has tapered off.”

However, directors of the herbarium and arboretum said Tucker’s gift will ensure a long-lasting legacy for his many contributions to a better understanding of oaks and other plants.
of technological evolution rendering a class obsolete. “In 1990, we offered a class in alternatives to radioactive labelling, which were newly developed,” she says. “The health, environmental, disposal and monetary costs of using radioactive labels had become apparent, and I felt it was important to introduce these techniques.” Today the techniques are standard, and the course isn’t offered separately, its content having been incorporated into the biotechnology program’s other classes.

Enter polymerase chain reaction (PCR), a technique used to make numerous copies of a specific segment of DNA quickly and accurately.

“By the early 1990s, PCR was really taking off,” says McGloughlin. “I contacted someone I knew at Perkin-Elmer, who was willing to provide equipment and teach a class.”

McGloughlin continues, “We still offer an advanced PCR class and it’s one of the most highly subscribed to. We constantly update it because the technology is constantly evolving.” She laughs as she recalls that a few years ago several employees from Chiron, a biotechnology firm, attended the class. “The Chiron employees were essentially coming from where PCR originated because Chiron took over Cetus, the company that invented PCR. So it was funny that they came here to learn the technique. Apparently people in the company were simply too busy to teach the technique.”

She adds, “We offered in situ PCR for two years, but the technique was so system-specific and temperamental that it didn’t lend itself to a generic lab course. A course on carbohydrate research didn’t garner enough interest to warrant the time and energy involved in offering it. So in addition to courses that became obsolete, courses that just didn’t work out have been a part of the program’s growth.”

McGloughlin then took the initiative to discover what type of biotechnology instruction was needed.

“I thought we should offer a protein analysis class,” says McGloughlin, “although the first time we offered it not many people enrolled. Since then people have moved from genomics to proteomics [quantifying all the proteins expressed at any given time in a cell] and the enrollment has increased. The class has also evolved from basic protein analysis— isolation, purification, and characterization—to true proteomics using 2-D gel analysis and advanced mass spectrometry. We teach the class in conjunction with the UC Davis Molecular Structure Facility, which helps familiarize people with the powerful technology that’s available on this campus.”

A burgeoning new discipline motivated McGloughlin to expand course offerings in 1995-96. “It became clear to me that we needed to focus on bioinformatics, which addresses how to electronically store, organize, and access the massive datasets being generated in the life sciences,” says McGloughlin. “For so long biologists went into biology because they were math averse—we can’t afford to be that way any longer.”

The initial bioinformatics course was a survey course and McGloughlin discovered it wasn’t focused enough.

“For the bioinformatics course we had a huge spectrum. At one end were biologists who wanted to know something about bioinformatics but didn’t want to know what happens inside the black box; they didn’t want to know how to program computers. At the other end were the computational people who wanted to know more about biology, and then there was a whole bunch of people in the middle who wanted to know a bit of both.” In 2001, McGloughlin therefore split up the one bioinformatics class into two sections, each of which covers a different aspect of the subject.

Overall the fast-paced courses receive excellent evaluations. “The content of the courses usually challenges the students,” says McGloughlin, “and often they learn more than they had expected to.” She laughs again as she says, “A woman in the protein analysis class said her head hurt afterward, but she gave us a great evaluation.”

Depending on pre-enrollment, McGloughlin plans to offer the following courses in summer 2001:

- In Situ Diagnostics and Analysis
- Confocal Microscopy
- Advanced Polymerase Chain Reaction Techniques
- Bioinformatics I: Instrumentation and Biological Samples
- Bioinformatics II: Databases, Visualization, Data Mining and Integration, Algorithms and Image Processing
- Protein/Proteome Analysis

Information about enrollment, costs, and course content is available at http://www.biotech.ucdavis.edu/courses/new_courses.htm.
CARL SCHMID: A STORY WITH REPETITIVE ELEMENTS

The Christmas he was 7 years old, Carl Schmid was walking with his father when he spied a shiny chemistry set displayed in a store window. Schmid asked if he could have the set; his father replied, “No, you have to become a chemist to have that.” The younger Schmid immediately thought, “Then I’ll become a chemist.”

His resolve never wavered. “Chemistry was my childhood hobby,” Schmid says. “I set up a home lab and cut grass to buy chemistry sets. My friends and I made explosives and concocted our own experiments. It’s something I really wanted to do.”

As an undergraduate, Schmid attended Drexel Institute, Philadelphia, Pa., where students attend school for six months and work for six months. His job not only made college affordable, but also exposed him to the research that would become a primary interest. “I was placed in a laboratory and became interested in nucleic acids, an interest that led me to pursue my doctoral studies under John Hearst, who was studying DNA structure using physical methods, at UC Berkeley.”

After receiving his doctorate in biophysical chemistry in 1971, Schmid took a post-doctoral position at California Institute of Technology in Pasadena, where he became interested in studying eukaryotic genome structure at a time when sequencing and cloning techniques had not yet been developed. He continued his post-doctoral studies at UC Davis “with the idea,” says Schmid, “that I’d study the structure and organization of the human genome using physical methods developed at Cal Tech.”

Schmid became a faculty member in UC Davis’ Chemistry Department in 1973. His research on DNA structure led, in 1990, to a joint appointment in the chemistry department and Department of Genetics (now the Section of Molecular and Cellular Biology).

Since the late 1960s scientists had been aware that the eukaryotic genome contained repetitive DNA sequences. The prevailing theory was that many distinct families composed the repetitive DNA, each distinct family having a few thousand members interspersed throughout the genome.

Careful analyses carried out by Schmid and his laboratory revealed, in 1979, a situation very different from the prevailing theory: a major fraction of the repetitive sequences belonged to a single family—the Alu family, which appeared to constitute about five percent of the human genome.

Walter Eckhart, a molecular biologist with The Salk Institute, noted in 1981, “His [Schmid’s] recent work on interspersed sequences in the human genome has been a major contribution to a particularly interesting and important area of modern genetics. It has won him international recognition and has helped to advance the work of many others in the field.”

Most scientists believed the ubiquitous Alu repeats were purposeless—along with other types of DNA sequences that don’t code for genes, they fell under the rubric “junk DNA”—but in 1998 Schmid proposed the controversial theory that Alu repeats are activated when cells are damaged in some way, for example by heat, toxic compounds or lack of essential nutrients, and help repair damage by controlling genes that make proteins.

“We found that these repeating elements are expressed, normally at very low levels, but when a tissue is stressed, their expression increases,” says Schmid.

The recent publication of the human genome maps stimulated a reexamination of Schmid’s hypothesis.

“There’s tremendous excitement now that the genome has been sequenced,” says Schmid, “and it’s been observed that Alu repeats are extremely abundant throughout the genome, and are often found near genes that code for proteins.”

In fact, the maps show that Alu repeats make up 10 percent of the genome—twice as much as was previously supposed.

In regard to the widespread presence and strategic placement of Alu repeats, Francis Collins, director of the National Human Genome Research Institute, was quoted in a New York Times article as saying, “…the natural conclusion is, this part of our junk DNA isn’t junk.”

Schmid comments, “I can’t say at this point that my theory is right or wrong, but the new genome maps certainly have intensified interest in my laboratory’s research.”

Prescott Deininger, Zimmerman Chair for Cancer Research at Tulane University’s School of Public Health and Tropical

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Kevin A. Morano, Ph.D. Microbiology, 1996, is currently an assistant professor in the Department of Microbiology and Molecular Genetics at the University of Texas Medical School in Houston. He conducted his doctoral research in Professor Daniel Klionsky's laboratory (Klionsky is presently with the University of Michigan) studying targeting and assembly of vacuolar proteins. He continued his education with postdoctoral studies in the Department of Biochemistry at the University of Michigan Medical School (1996-2000), studying yeast stress-response mechanisms.

Morano is currently studying the functions of a class of proteins called “molecular chaperones,” which help proteins fold in the cell. Many important cellular regulatory proteins are very unstable and require a protein chaperone called Hsp90 to protect them. Says Morano, “My laboratory is interested in how the cell in turn regulates the function of the chaperones themselves. We’re also using the latest in DNA microarray technology to identify new stress genes in the model eukaryotic cell Saccharomyces cerevisiae, or baker’s yeast. Many of these genes have close human homologs, and by studying the genes in yeast, we may learn about how they are recruited for ‘stressful’ pathological states in our own cells, like cancer and aging.”

Jason Bradford, B.S., Biological Sciences, 1992, received his Ph.D. in evolutionary and population biology from Washington University, St. Louis, Mo. Says Bradford, “My current position is research associate at the Missouri Botanical Garden in St. Louis. I’m also a course instructor in ecology at Washington University.

“I was traveling in New Caledonia, in December 2000, on a grant from the National Geographic Society to study the systematics and pollination biology of a family of flowering plants, Cunoniaceae, that I specialize in. Along with me was Barry Donovan from New Zealand, who knows more about pollination biology than I do, and is an expert on the bees of New Caledonia. Barry received his doctorate from UC Davis in 1969 in entomology.

“While staying in a small motel in the northern town of Koumac, Barry and I met Mike Irwin. It turns out that Mike...
was there to study a group of flies he is doing a worldwide monograph on, and he also graduated from UC Davis—with a B.S. in entomology in 1963. He also has a Ph.D. in entomology from UC Riverside and is currently a professor at University of Illinois.

“My wife Kristin Bradford (née Sparks) also graduated from UC Davis in 1992 with a B.S. in physiology. She was the division’s first student commencement speaker. She now has a medical degree from University of Vermont and is finishing her residencies here in St. Louis (family practice and preventive medicine). We plan to move back to Davis in July 2001 with our twin boys, Curtis and Davis, who will be 2 1/2 years old by then.”

Faculty

The Botanical Society of America awarded its 2000 Merit Award, its highest honor, to Leslie Gottlieb, a professor in the Section of Evolution and Ecology. An announcement in Plant Science Bulletin, the society’s newsletter, described Gottlieb as “one of the most influential plant evolutionary biologists over the past several decades.” The award committee chair, University of Wisconsin genetics professor John Doebley, cited three of Gottlieb’s publications as classics, including a 1984 article in American Naturalist that “has been called one of the most important papers in plant evolutionary biology during the past half century.” However, Doebley added that Gottlieb’s “greatest contribution may have come through his influence on the careers and research of a substantial number of plant evolutionary biologists, including many of the people most active in this field today.”

In Memoriam

UC Davis exercise biologist Paul Molé, whose research contributed to an understanding of how muscles function during exercise, died on January 20 of complications following a heart attack. He was 62.

Molé became ill on Jan. 8 while teaching a class. Thanks to prompt action by his teaching assistants, he was taken to Sutter Memorial Hospital and later transferred to the UC Davis Medical Center in Sacramento. Although doctors were able to remove a blood clot from a coronary artery, his condition deteriorated, and he died early Saturday morning.

Molé’s main research interest was in skeletal muscle metabolism, and how it responds to exercise, said UC Davis Professor Emeritus Ed Bernauer, a friend and colleague for more than 40 years.

“He reanalyzed much of the important documented research, and formulated a mathematical model that challenged the accepted view,” said Bernauer. While the conventional view held that carbohydrate, not fat, was the primary fuel for muscles, Molé believed that fat played a greater role earlier in exercise, according to Bernauer. He then went on to test his ideas using magnetic resonance imaging (MRI) techniques.

“He’ll be sorely missed,” said Tom Jue, a biochemist in the School of Medicine who worked closely with Molé. Using MRI technology developed in Jue’s laboratory, they could look inside an athlete’s limb to see how the muscles used oxygen and fuel during exercise. As a physiologist with expertise in muscles, Molé’s contribution was very important in helping to develop the technology, said Jue. Eventually, the same technology might be used to study heart disease, he added.

Molé was vice chair of the Department of Exercise Science and held an adjunct appointment at the Department of Physical Medicine and Rehabilitation. He was a faculty member of the graduate groups in exercise biology, nutrition and physiology.

Molé played a pivotal role in the recent restructuring of the exercise biology program, and was actively involved in recruiting new faculty, said department chair Chuck Fuller.

“We’re going to miss his insight as we build for the future,” said Fuller.

“He was an intense and committed educator, who felt it was the obligation of the professor to bring students to the highest level of understanding,” said Bernauer. “Paul was always challenging his students, always pushing them to think,” said Fuller.

Brought up in Jamestown, N.Y., Molé entered the University of Illinois, Urbana-Champaign, on a football scholarship, graduating in 1960. He stayed at Illinois to complete a M.S. in physical education and a Ph.D. in physiology. He joined UC Davis in 1977.

Molé was a Fellow of the American College of Sports Medicine, and a member of the American Physiology Society and the New York Academy of Science. He served as president of the Southwest chapter of the American College of Sports Medicine from 1999 to 2000.

Molé loved the outdoors, whether walking in the woods, fishing or gardening, said his wife of 42 years, Patty. He was a keen amateur photographer. His parents were bakers, and he liked to bake and cook, making fresh bread every weekend, she said.

He is survived by Patty; their three children, Pam, of Oklahoma, Greg, of Pittsburgh in the Bay Area, and Michael, of San Jose; and five grandchildren. In his freshman year on a football scholarship, Molé told his coach that he was marrying Patty, his high-school sweetheart. The coach told him he could either get married or play football, but not both. Molé responded by giving up football and taking up fencing, joining a team that went on to win the Midwestern Big Ten championship, an achievement that typified his determination and persistence, said Bernauer.
Smietana supported himself by programming computers. He thus possesses both biological and computational perspectives. Smietana has been associated with the biotechnology industry for more than 18 years; while with Ciphergen Biosystems and GeneLogic he created novel methods for integrating protein and DNA expression data with public and private clinical and genomic databases. For the past three years, he has taught the summer bioinformatics short courses.

Underscoring the need to think big, Smietana talks about the direction in which the life sciences industry is headed. "I want students to be aware of the scaling up of technologies in industry," he says. "As an example, LumiCyte is going to have 20, perhaps 30 or 40 instruments, with multiple sites throughout the world, collecting information on proteomic biochips. Again, the amount of information is staggering—we’re talking about terabytes of information."

According to Smietana, what this translates into is a need for people who know how to design complicated, integrated experiments.

"We’re moving into a time when we’ll need to integrate our knowledge of genes with our knowledge of proteins," says Smietana. "Genes don’t mean very much without the context of proteins and vice versa. So the scope of your experiment has to change. You now have to consider bringing in more information than you ever have before. That means you’re going to have to learn something about the tools that are out there. A student may study one protein for her doctoral research, but we now have the ability to study sets of proteins."

When asked how undergraduates can prepare themselves for careers in bioinformatics, Smietana replied with a brief anecdote. "I was recently at a meeting with representatives from Genentech, DoubleTwist, Applied Biosystems, and Iconics," he says. "Asked for description of an ideal candidate for a position in bioinformatics they responded, ‘A full professor in biological sciences with 20 years experience in the computer field.’ We know that person doesn’t exist, so how can you parlay that down? The best strategy for an undergraduate is to take a diverse program."

And remember: think big.