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Do-It-Yourself Genetic Engineering

By JON MOOALLEM

IT ALL STARTED with a brawny, tattooed building contractor with a passion for exotic animals. He was taking biology classes at City College of San Francisco, a two-year community college, and when students started meeting informally early last year to think up a project for a coming science competition, he told them that he thought it would be cool if they re-engineered cells from electric eels into a source of alternative energy. Eventually the students scaled down that idea into something more feasible, though you would be forgiven if it still sounded like science fiction to you: they would build an electrical battery powered by bacteria. This also entailed building the bacteria itself — redesigning a living organism, using the tools of a radical new realm of genetic engineering called synthetic biology.

A City College team worked on the project all summer. Then in October, five students flew to Cambridge, Mass., to present it at M.I.T. and compete against more than 1,000 other students from 100 schools, including many top-flight institutions like Stanford and Harvard. City College offers courses in everything from linear algebra to an introduction to chairside assisting (for aspiring dental hygienists), all for an affordable $26 a credit. Its students were extreme but unrelenting underdogs in the annual weekend-long synthetic-biology showdown. The competition is called iGEM: International Genetically Engineered Machine Competition.

The team's faculty adviser, Dirk VandePol, went to City College as a teenager. He is 41, with glasses, hair that flops over his forehead and, frequently, the body language of a man who knows he has left something important somewhere but can't remember where or what. While the advisers to some iGEM teams rank among synthetic biology's leading researchers, VandePol doesn't even teach genetic engineering. He teaches introductory human biology — "the skeletal system and stuff," he explained — and signed on to the team for the same reason that his students did: the promise of this burgeoning field thrills him, and he wanted a chance to be a part of it. "Synthetic biology is the coolest thing in the universe," VandePol told me, with complete earnestness, when I visited the team last summer.

The first thing to understand about the new science of synthetic biology is that it's not really a new science; it's a brazen call to conduct an existing one much more ambitiously. For almost 40 years, genetic engineers have been decoding DNA and transplanting individual genes from one organism into another. (One company, for example, famously experimented with putting a gene from an arctic flounder into tomatoes to make a variety of frost-resistant tomatoes.) But synthetic biologists want to break out of this cut-and-paste paradigm altogether. They want to write brand-new genetic code, pulling together specific genes or portions of genes plucked from a wide range of organisms — or even constructed from scratch in a lab — and methodically lacing them into a single set of genetic instructions. Implant that new code into an organism, and you should be able to make its cells do and produce things that nothing in nature has ever done or produced before.

As commercial applications for this kind of science materialize and venture capitalists cut checks, the hope is that synthetic biologists can engineer new, living tools to address our most pressing problems. Already, for example, one of the field's leading start-ups, a Bay Area company called LS9, has remade the inner workings of a sugar-eating bacterium so that its cells secrete a chemical compound that is almost identical to diesel fuel. The company calls it a "renewable petroleum." Another firm, Amyris Biotechnologies, has similarly tricked out yeast to produce an antimalarial drug. (LS9, backed by Chevron, aims to bring its product to market in the next couple of years. Amyris's drug could be available by the end of this year, through a partnership with Sanofi-Aventis.) Stephen Davies, a synthetic biologist and venture capitalist who served as a judge at iGEM, compares the buzz around the field to the advent of steam power during the Victorian era. "Right now," he says, "synthetic biology feels like it might be able to power everything. People are trying things; kettles are exploding. Everyone's attempting

magic right and left."

Genetic engineers have looked at nature as a set of finished products to tweak and improve — a tomato that could be made into a slightly better tomato. But synthetic biologists imagine nature as a manufacturing platform: all living things are just crates of genetic cogs; we should be able to spill all those cogs out on the floor and rig them into whatever new machinery we want. It's a jarring shift, making the ways humankind has changed nature until now seem superficial. If you want to build a bookcase, you can find a nice tree, chop it down, mill it, sand the wood and hammer in some nails. "Or," says Drew Endy, an iGEM founder and one of synthetic biology's foremost visionaries, "you could program the DNA in the tree so that it grows into a bookshelf."

Endy is part of a group of synthetic biologists that is focused on building up basic tools to make this process faster, cheaper and less research intensive, so that even the most sophisticated custom-built life forms can be assembled from a catalog of standardized parts: namely, connectable pieces of DNA called BioBrick parts, which snap together like Legos. Ideally you wouldn't even need to know anything about DNA to manipulate it, just as a 5-year-old doesn't need to understand the chemical composition of the plastic in his Legos to build a fortress on the living-room carpet.

With the field still in its infancy, and with such monstrously ambitious work ahead of it, you never really hear the word "failure" at iGEM. Some teams do manage genuine breakthroughs. (One of the most successful teams in 2009, drawn from two universities in Valencia, Spain, engineered a synthetic yeast that lights up in response to electricity, with which they might construct a computer screen made of yeast cells instead of digital pixels — a living LCD.) But students aren't necessarily expected to build a perfectly functioning living machine in one summer. More important at this stage are the tools and the techniques they generate in the process of trying.

Over the past five years, iGEM teams have been collaboratively amassing a centralized, open-source genetic library of more than 5,000 BioBricks, called the Registry of Standard Biological Parts. Each year teams use these pieces of DNA to build their projects and also contribute new BioBricks as needed. BioBricks in the registry range from those that kill cells to one that makes cells smell like bananas. The composition and function of each DNA fragment is cataloged in an online wiki, which iGEM's director calls "the Williams-Sonoma catalog of synthetic biology." Copies of the actual DNA are stored in a freezer at M.I.T., and BioBricks are mailed to teams as red smudges of dehydrated DNA. Endy showed me a set stuck to paper, like candy dots.

Still, the real legacy of iGEM may end up being the future synthetic biologists it is inspiring. There was an irrepressibly playful atmosphere around the weekend-long iGEM Jamboree at M.I.T. — students strode around in team T-shirts or dressed up as bacterial mascots — and each year the winning team flies home with the BioBrick grand-prize trophy, a large aluminum Lego, which is passed from champion to champion like the Stanley Cup. IGEM has been grooming an entire generation of the world's brightest scientific minds to embrace synthetic biology's vision — without anyone really noticing, before the public debates and regulations that typically place checks on such risky and ethically controversial new technologies have even started.

City College, the first two-year college to enter a team at iGEM, is not the place to go if you want to see synthetic biology's cutting edge. But it turns out to be an ideal place to understand the can-do fervor propelling the science forward. The question was never whether Team City College would win this year's iGEM. It would absolutely not win. The question was how it managed to get there at all.

Of all the City College students, Colby Sandate seemed the most enthralled with synthetic biology; he often drove around the Bay Area to attend talks by its leading researchers and provocateurs or to visit start-ups. He hoped to make a career in the field, he told me, and felt lucky to be a part of the generation that would get in on its ground floor. "It's a chance to be part of something bigger than ourselves," he said. "A real modern scientific movement."

Sandate, who is 21, is half indigenous Mexican, half Italian. He was working 20 hours a week selling Kiehl's skin-care products to women in upscale Pacific Heights, but even so he emerged as the de facto leader of the City College team,

shouldering a lot of the bureaucratic responsibilities and always projecting a low-key confidence in the lab. “His temperament is just indestructible,” VandePol told me one morning.

It was the first week in September, and the team was reconvening after a two-week break. City College closed its building for most of August, exiling the members of the synthetic-biology team from the unoccupied basement classroom they had commandeered as a lab (the school is not a research institution — there are no real laboratories). The school had been facing escalating financial trouble all year, and now with the fall semester starting and classrooms filling up, all it could offer the team members was a run-down greenhouse on the top floor of the science building. It was filled with plants, flies and compost tubs and smelled of mildew and loam: not the sterile environment their work required. So they began squatting in whatever classroom happened to be open on a given day, wheeling their materials around the halls on carts.

Teams at most schools pay students to work on their projects; some have budgets as high as $90,000. At the iGEM Jamboree, the backs of some team shirts overflowed, Nascarlike, with their sponsors’ logos, including those of a few multinationals like Monsanto and Merck. The City College team had rustled up a budget of $18,000. (A school administrator knew someone who knew the widow of a Berkeley scientist and Levi-Strauss heir.) Almost everything the team had was either donated or borrowed. An educational nonprofit lent it some equipment, and the students took frequent trips to a depot an hour south, where biotech start-ups ditch their old glassware. There were no stipends, and the students were balancing their work on the battery with jobs and their regular coursework. It made for an unpredictable, rotating cast.

But by early fall the core group that would travel to M.I.T. established itself. In addition to Sandate, there was the team’s founder, Leeza Sergeeva, a deadpan 19-year-old from Moscow; Angela Brock, 34, with a bleached, punk haircut, who came back to school to study electrical engineering after dropping out 10 years ago; and Bertram Lee, 47, a high-spirited man who wore his pants high on the waist and short at the ankles. Lee spent a decade designing databases in the financial sector, then took up science somewhat spontaneously after his parents passed away. Finally there was Bowen Hunter, a plucky 27-year-old certified massage therapist who went to a Southern Baptist high school in Texas that taught creationism instead of evolution and now wanted to get a master’s and teach in City College’s biotech track.

From a technical standpoint, the design of the team’s battery was relatively straightforward compared with other iGEM projects, but it turned out to be ambitious in its own way. Two glass containers, the size of cider jugs, would be connected by a glass tube. Each contained a different species of bacteria, living in a liquid medium. The bacteria on the right side, R. Palustris, are photosynthetic, converting sunlight into sugar, which they need to survive. The other bacteria also subsist on sugar but can’t generate their own; they use sugar as energy to create a small electric charge. Both types of bacteria exist, as is, in nature; the team spent a lot of time researching online for the best-suited species and ones they could easily obtain. VandePol fetched a particularly good strain of R. Palustris from a lab at M.I.T. when he flew there for an iGEM teachers’ training last spring, and the team bought the other bacteria, first discovered at the bottom of a bay in Virginia, for $240 through the mail.

The idea was to build a bacteria-based battery that could be powered entirely by the sun. To do that, the team would redesign the photosynthetic R. Palustris so that it released some of the sugar it made and sent it through the tube to fuel the electricity generation of the bacteria on the other side. The students would need to re-engineer R. Palustris to give up its food — something that in nature would be totally nonsensical. They had a long list of tasks, but this was the pivotal one: give R. Palustris a leak.

The story of iGEM and, to some degree, the vision of synthetic biology that it champions, begins not with biologists but with engineers. From the beginning, the approach was rooted less in the biologist’s methods of patient observation than in the engineer’s childlike love of building cool stuff and hyperrational expectations about the way things ought to work.

Drew Endy came to M.I.T. as a bioengineering fellow in 2002 at the age of 32. He now teaches at Stanford and is probably the field’s most voluble and charismatic spokesman. “I sort of Facebook-stalk him,” I overheard a student say at the jamboree. (Last month, the National Science Foundation financed the creation of a full-scale BioBrick part factory in the Bay Area, called the Biofab; Endy is a founding director.) At M.I.T., Endy found a group of colleagues — like him, all originally engineers by

training — who were disappointed with how unmethodical a field that was termed “genetic engineering” appeared to still be: its major successes were more like imaginative, one-off works of art than systematic engineering projects. As Endy told me, “I grew up in a world where you can go into a hardware store and buy nuts and bolts, put them together and they work.” Just as you tell a computer to add 2 and 2 and know you’ll get 4, Endy said, you should be able to give a cell simple commands and have it reliably execute them — and explaining this, he still managed to sound honestly flummoxed that something so absolutely logical wasn’t actually true; his approach to the living world is astonishingly Spock-like. “Biology is the most interesting and powerful technology platform anyone’s ever seen,” he said. “It’s already taken over the world with reproducing machines. You can kind of imagine that you should be able to program it with DNA.”

Arguably this has been an implicit dream of genetic engineering all along. But starting in the mid-’90s, synthetic biologists concluded that we had amassed enough knowledge about how genomes work and developed enough tools for manipulating them that it was time to actively pursue it. In 2003, Endy formed a partnership with three other like-minded engineers at M.I.T., Gerald Sussman, Randy Rettberg and Tom Knight. Rettberg, who now directs iGEM, had absolutely no background in biology until, after retiring as a chief technology officer at Sun Microsystems in 2001, he started reading textbooks and hanging around Knight’s lab; the two friends worked early in their careers on designing computers. Knight had already developed the concept of BioBrick parts and a method for connecting them.

The four men decided that rather than spend decades figuring out how to turn life into the predictable machinery they wanted it to be and then teaching that to their students, they would enlist the students to help. They taught a monthlong course challenging teams of students to design E. coli that “blinked” — that is, generated fluorescent light at regular intervals. That first experimental class rapidly evolved, by 2006, into an iGEM Jamboree involving 35 schools. And from there, Endy told me, “this thing goes international fast.”

It’s easy to understand what makes synthetic biology alluring to undergrads. For biology students, iGEM is a chance to creatively design the kind of powerful biological systems inside organisms they’ve spent so many years studying. For engineers, it’s a chance to work with the most awesome material around: life. It’s also a rare opportunity for students to direct their own research. Experiments done for science classes are usually predetermined to work. Here, as Bowen Hunter put it, “You’re not just following instructions; you’re paving a way.” Consequently, many schools’ iGEM teams are initiated by students, almost as extracurricular clubs for the summer, not by professors or provosts. Endy told me, “We have now, in a bottom-up, grass-roots fashion, de facto installed a genetic-engineering curriculum for the future of our field in 120 schools worldwide.”

By now, many schools have taken a proactive approach, developing “iGEM boot camp” courses and smaller, intramural iGEM jamborees in advance of the competition. A public high school in San Francisco teams seniors with mentors from the University of California, San Francisco to compete. “I’ve just never seen an idea that galvanizes the excitement of young students as much as this,” says Wendell Lim, the team’s adviser. At Imperial College London, strong showings at the iGEM Jamboree have contributed to the growth of a full-fledged synthetic-biology institute. Or consider the case of the Slovenian iGEM team, the most intimidating squad coming into last fall’s jamboree and also the hardest to miss, having forgone mere team T-shirts for severe, blue athletic jerseys that made the dozen young Slovenians seem capable of sprinting 200 meters or throwing a discus at a moment’s notice. “I think the last two years, we have 100 percent, beyond doubt, the best shirts,” the team’s adviser, Roman Jerala, told me.

Slovenia had won the BioBrick trophy in two of the past three iGEMs, including the previous fall, when it produced a possible vaccine for a bacteria that causes stomach ulcers, presenting promising data in mice. The team is covered consistently by the Slovenian media, and Jerala had recently lectured about synthetic biology to the Slovenian National Assembly. A television network named him one of Slovenia’s seven most influential people.

The students at City College splurged. One day last summer, they ordered a brand-new $600 voltage meter, so that if they got the battery up and running, they could measure the electricity it generated. Their prototype might only light an LED, but by scaling up the two chambers of bacteria you could, in theory, build a credible tool for solving the world’s energy crisis — at

lower cost than conventional solar panels. Sergeeva envisioned a smaller version to power space probes.

The voltage meter was the team's only piece of new equipment, and its arrival one day last September was stirring. Though the team was woefully behind schedule, morale was high, and VandePol clearly wanted to keep it that way. "Isn't this a little honey?" he said, slipping the yellow machine out of its box. "Let's measure the voltage of something!"

He had Sandate hold the meter's leads in each hand. Then he grabbed the lid of the Styrofoam cooler in which they kept their vials of DNA and started rubbing it against Sandate's sweater, trying to get some static going. The meter didn't move. Sandate looked at the soles of his sneakers. "Maybe if I'm not grounded," he said. He stood on a chair. VandePol kept rubbing. Still nothing.

This was about how things were going for Team City College. Across the room, Bowen Hunter was, as usual, toiling away in front of the P.C.R. machine, a desktop appliance that looked like some 1970s conception of a futuristic food processor. P.C.R., or polymerase chain reaction, has been a key tool in genetic engineering since the late 1980s — a way to copy, rearrange or stitch together particular sequences of DNA by alternately heating and cooling the DNA to break and reform its chemical bonds. Hunter was carefully pipetting various fragments of other DNA, called primers, into the top of the machine. The team had been painstakingly experimenting with the right combinations of primers, as if perfecting a recipe, to copy a particular gene. Hunter had to add the contents of more than 100 different pipettes before she could run the machine, initiating a number of various reactions, and she sat there in her lab coat and goggles for hours, ripping open sterile pipette tips, chucking each used one into a plastic hazmat bin in front of her.

The team had done some more research and discovered that there are species of bacteria that already have holes in their cell membranes through which sugar passes; those bacteria all use the holes to let food in, but they could, theoretically, be made to do the reverse. It was exactly the design feature that Team City College needed to give its R. Palustris. They had already made multiple attempts to first pull that particular gene out of one bacterium and tweak it in a specific way to turn it into an easily connectable BioBrick part. Then they would try to insert that into R. Palustris.

Most iGEM teams' designs involve many more manipulations of DNA; some teams create a dozen new BioBricks during the summer, but this hole-maker would be City College's sole contribution to the registry. Even if the battery never worked, another synthetic biologist, 50 years from now, might stumble upon this custom-made part, take it off the shelf and put it to a totally different use in an organism he or she was designing. That is, if the City College students ever managed to actually create the BioBrick. If they didn't design the primers correctly, a reaction would fail. If Hunter's arm wasn't totally steady as she deposited those chemicals into the machine, a reaction would fail. If flecks of her skin or her hair — or any other stray DNA in the room, for that matter — fell into the machine, a reaction would fail. And reactions were failing — again and again, for most of August and into the fall.

This work is not nearly as big a stumbling block for more typical iGEM teams. In fact, some better-financed teams outsource the job to professional gene-synthesis companies with superior, industrial-scale equipment. The cost of synthesizing genes has dropped tremendously in the last five years. (DNA is essentially an intricate chain of four different chemical compounds, each represented by a letter; a gene can be thousands of letters long. You can now send a sequence of those letters to companies like Blue Heron Biotechnology, outside Seattle, and get the actual gene back in the mail for a dollar, or less, per letter.) Across the bay from City College, a University of California, Berkeley iGEM team was building a piece of computer software that allowed it to design genetic parts by dragging and dropping DNA sequences together on the screen. Then, with the click of a button, the software fed instructions to a liquid-handling robot in their lab that executed various reactions and assembled each genetic part they needed. It was like when you line up songs on iTunes and burn the playlist on a CD. "We're making way more DNA's than we ever have before, and we couldn't have done it without the robot," the Berkeley team's adviser told me.

City College didn't have a robot. They had Hunter. And what astounded me as I continued to visit the team was how persistent she and everyone else remained despite the fact that — by any objective measure — their battery remained a failure. With only a few weeks to go, at 4 o'clock on a sunny Friday afternoon, the week before midterms, I found them pounding

away at all dimensions of the project. Hunter was now working with the P.C.R. machine for hours at a time in a storage closet, the only space she could consistently find available.

Even if the battery wasn't working, iGEM itself was. With the limits of what's possible still totally unclear in synthetic biology, what the field may need most of all — what will move it forward faster — is a global mob of young people slogging away in their labs to construct stuff plucked from the edges of their imaginations. A new field needs failures to analyze and successes to build on. Moreover, if the goal is to make life easier to manipulate — requiring less time, money and, ultimately, expertise — "the fact that a community college can participate," Drew Endy noted, "is a sign that we are succeeding."

The rise of synthetic biology only intensifies ethical and environmental concerns raised by earlier forms of genetic engineering, many of which remain unsettled. Given synthetic biology's open-source ethic, critics cite the possibility of bioterror: the malicious use of DNA sequences posted on the Internet to engineer a new virus or more devastating biological weapons. ETC Group, an international watchdog that has raised complicated questions about synthetic biology since its earliest days, also warns of the potential for "bio-error": what unintended and unimaginable consequences might result from deploying all these freely reproducing, totally novel organisms into the world? What if those living machines don't work exactly as planned? "In a way, you don't have to have a working product to sell it," says Jim Thomas, a senior researcher at ETC Group. "You just have to have a product that seems to work long enough to get into the open market." And, Thomas adds, as corporations continue to invest in organisms that turn biomass into fuel or plastics, otherwise unlucrative crops will suddenly be commoditized as feedstock for those synthetic organisms — requiring more land to be cultivated and potentially displacing food crops or people.

"This absolutely requires a public and political discussion," Thomas told me. "It's going to change the alignments between very large corporations. It's going to change the ownership and patenting of life forms. The field is growing at such a speed and industrial money is flowing into it at such a speed — and here you have very excited, smart, clever young people becoming wedded to these techniques. The worry is, there's not a lot of space left for reflection."

Most students I met at iGEM said they were attracted to synthetic biology because of the immense good it might accomplish and had spent their summers engineering very altruistic microbes: ones that generate cheap alternative energy, attack tumors or deliver pharmaceuticals within the body, detect fertilizer runoff in drinking water, reveal the location of land mines or, in the case of Stanford's team, wipe out irritable-bowel syndrome. iGEM has begun to require students to consider any ethical or safety questions their projects raise, and Endy seems particularly intent on making sure that these issues, as they pertain to the field in general, are discussed publicly.

Still, the spirit of the competition is geared toward exuberance, not introspection. At the closing ceremonies, iGEM's director, Randy Rettberg, told everyone that he was counting on them to "spread synthetic biology everywhere." He invoked, as he does constantly, his role in pioneering the Internet 40 years ago and explained, "I think that over the next 40 years synthetic biology will grow in a similar way and become at least as important as the Internet is now and that you will be the leaders, that you will form the companies, that you will own the private jets and that you will invite me for rides."

After Rettberg's speech, the 2009 BioBrick trophy was ceremoniously awarded to the Cambridge University team, developer of "E. Chromi": E. coli that is programmable to turn one of five colors when it detects a certain concentration of an environmental toxin. After the announcement, the Cambridge squad strode out onto the lawn in front of the auditorium, formed a human pyramid and posed for photos around the big silver Lego.

Team City College stood a few yards behind them with understated pride, reveling in the intellectual contact high and collegiality of the entire weekend — even though, in the end, the team never managed to produce a functioning BioBrick for the registry and was thus disqualified for the most basic form of commendation, an iGEM bronze medal. "That was sad," one judge, a Harvard Ph.D. candidate named Christina Agapakis, later told me. "I really wanted to give them a medal. They were so excited and so motivated despite all the challenges they faced. I really liked them. I was definitely rooting for them as underdogs."

In fact, the students from City College heard this from people, spontaneously, throughout the weekend: as one man who approached Colby Sandate put it, they embodied the audacity and the grit that iGEM is supposed to be about. The competition, after all, is itself a machine, engineered to absorb enthusiastic young people and produce synthetic biologists. “I was like, ‘Really?’ ” Sandate told me. “Nobody’s ever complimented us that much before.” He had chosen to genuinely embrace Team City College’s status as the Bad News Bears of synthetic biology. Like the head of a small start-up, he was already lining up equipment, lab space and seed money for the next year.

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This article has been revised to reflect the following correction:

Correction: February 14, 2010
An article on Page 40 this weekend about synthetic biology misstates the cause of stomach ulcers for which a possible vaccine is being produced by a team of Slovenian students. The vaccine would treat ulcers caused by bacteria, not by a virus.