Current Topics

Grand Ambitions Drive Early "Baby Steps" In Synthetic Biology

With synthetic biology, "don't believe the hype; we're taking baby steps and it's hard to get things to work the way you want," says James Collins of Boston University in Boston, Mass. "We're still like the Wright brothers, putting wood and paper together," adds Herbert Sauro of the University of Washington, Seattle. "This field has had its hype phase; it's time to deliver."

Hype, in a way, continues to drive synthetic biologists, even as they grow more careful about offering caveats about progress while remaining keen on describing their hugely ambitious agendas. That mix of humility and pride was integral to the atmosphere during a recent meeting, "Synthetic and Systems Biology," of the Forum on Microbial Threats, convened by the Institute of Medicine (IOM) Board on Global Health, and held last March in Washington, D.C. The IOM board, in part, is seeking advice as to how such research might serve biodefense needs as well as broader efforts to combat infectious diseases—or how it might lead to new risks. The prospects for help, board members learned, are great even if delivery dates are uncertain. Moreover, the near-term risks appear to have been overstated.

"We all have Craig Venter [of the J. Craig Venter Institute] and George Church [of Harvard University] envy," says meeting participant Andrew Ellington from the University of Texas, Austin. Compared to them, "the rest of us are hobbyists." Citing efforts by Venter and his collaborators to reconstitute bacterial cells with synthetic genomes (*Microbe*, August 2010, p. 326), he says, "Synthetic biology does not worry me a bit [because] 'boot-up' proves to be harder than synthesis."

In other words, inherent difficulties in making things work are a major safeguard in synthetic biology, setting a helpful barrier against dangers in its misuse. Thus, the making of microbial genomes, a process that is difficult but feasible, is only part of the challenge of producing a truly dangerous and novel designer pathogen. The bigger challenge is in making it work biologically. In the Venter case, proving a synthetic genome can work required a living cell that was a close cousin of the organism from which the genome had been crafted.

Ellington was in no way playing down what the Venter group achieved. However, he and others did mean to provide a context for assessing the biodefense risks that its success might pose. "I agree with Andy [Ellington] that it's hard to get things to work the way you want," Collins says. "We don't have enough intuition about biology."

An early vision of synthetic biology was that it would produce something like a "car-repair manual," says Paul Freemont of Imperial College in London, United Kingdom. The initial work entailed developing "data sheets of microbial parts" under the belief that, if properly "characterized," those parts could be incorporated into virtually any "design." Despite minor successes, that ambitious goal remains unmet. Says Sauro, "The parts are not well characterized, the in vivo context is not well understood, and that context changes most of the time—during experiments, adaptation occurs, our ability to measure [what occurs] quantitatively is crude, and we rarely report exactly what we did." Plus, he adds, "We're under pressure to get 'wow' results."

Nonetheless, Ellington and his collaborators are not so shy about their own undertakings, which seem to go beyond weekend tinkering. For example, he summarized recent efforts to manipulate and rearrange huge tracts of genes from microbial genomes, saying it now is possible to remove and reorganize substantial portions of genomes from different species of bacteria en route to creating "truly chimeric microorganisms." Putting it in more audacious taxonomic terms, he says, "We can now make '*Salmonella aureus*.'"

Church from Harvard also anticipates taking substantial leaps with synthetic biology as the springboard, with one line of pursuit involving efforts to incorporate "artificial" amino acids into proteins as a way of developing enzymes with novel catalytic capabilities, high efficiencies, and extended stability to enhance their usefulness in industrial applications. If that is not ambitious enough, he foresees developing synthetic ribosomes as one means for easing the flow of such amino acids into proteins.

Yet, without introducing artificial amino acids, it can be greatly challenging to understand what conventional amino acids, genes encoding them, and enzymes expressing them can do, suggests Bernhard Palsson of the University of California, San Diego. For instance, efforts to compute the phenotype of a microorganism

from its genotype prove to be "very, very difficult" and involve "many steps," he says. "These are very large data sets, and integrating them is a formidable challenge. But it's amazing we can get it about 75% correct just from the sequence . . . We've reached the point where data analysis is the rate-limiting step."

One unexpected bit of fallout from such efforts is that the "operon concept" may need reviewing because the first operons to be evaluated in this light prove far more convoluted than previously thought, Palsson says. This issue takes on considerable importance as researchers try to better understand how virulence traits and pathogenicity islands behave in different contexts—for instance, how microbial gene expression changes, and accounts for what happens, when *Escherichia coli* moves from being a pathogen of the urinary tract to act as a pathogen in the gastrointestinal tract.

More fundamentally for researchers in synthetic biology, the working definition of life can prove elusive, at least when someone tries to capture it succinctly and put it into simple practice, according to Gerald Joyce of the Scripps Research Institute in La Jolla, Calif. Studying stripped-down ribozymes to investigate self-sustaining reactions of biological materials, he and his collaborators can follow "self-sustained exponential amplification" reactions that appear to mirror in chemical terms the simplest of living, or life-like processes. Yet, he says, they prove "really boring" in large part because "there are no hidden variables in these systems." Life is more than replication with potentially heritable consequences, he suggests. It also requires the "capacity for development of novel functions—to be capable of [being] inventive."

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Tracking Tuberculosis in Zebrafish and via the Fur Trade in Canada

After being incorporated into host macrophage cells, *Mycobacterium tuberculosis* bacterial cells induce drug efflux pumps, apparently explaining how they so quickly develop tolerance to antibiotics, according to Jennifer A. Philips and Joel D. Ernst of New York University School of Medicine in New York, N.Y. Treating tuberculosis (TB) patients with pump inhibitors along with the usual antibiotics might provide a way to abbreviate the months of therapy typically required for such patients to overcome TB, they suggest. Details, based in part on studying how *Mycobacterium marinum* behaves in zebrafish, appear in the 1 April 2011 *Cell* (**145:**13–14). Separately, a genetic analysis of how TB spread from Europeans to native populations during the height of the Canadian fur trade, which began in 1710 and lapsed in 1870, suggests that relatively isolated populations of *M. tuberculosis* barely survived but then expanded markedly when environmental conditions permitted, according to Caitlin Pepperell at Stanford University School of Medicine in Stanford, Calif., and her collaborators. TB apparently thus spreads via two separate processes, one involving small numbers of infected people migrating into new areas carrying the disease in a "smoldering" state and the other involving sharp expansions in response to, say, changes that particular host populations face in terms of living conditions. "If generalizable, these migration dynamics can help explain the low DNA sequence diversity observed among isolates of *M. tuberculosis* and the difficulties in global elimination of TB," they point out. Details appear online in the April 4, 2011 *Proceedings of the National Academy of Sciences* (doi: 10.1073/pnas.1016708108).

Major Host Health Effects Ascribed to Gut Microbiome

Commensal gut bacteria apparently influence human health more than they are credited with, according to Jeremy Nicholson of Imperial College, London, England, who spoke during the symposium, "The Human Body as Supra-Organism, Microbial Observatory, and Ecosystem at Risk," part of the annual meeting of the American Association for the Advancement of Science, held in Washington, D.C., last February. The gut microbiome contains roughly 3.3 million genes, far more than the estimated 23,000 genes of its human host, he declares. "We're less than 1% human in terms of active genes in the body.

"A lot of noninfectious human disease is associated with abnormalities of the gut microbiota," Nicholson continues, including gastric ulcers, colon and other cancers, several autoimmune diseases, and type 2 diabetes. He also pointedly adds autism, schizophrenia, and hypertension to that list.

"We have found that there are highly significant correlations between [at least 6; possibly as many as 30] selected gut microbial metabolites and blood pressure, that probably have a pharmacological basis," Nicholson continues, noting these findings come from studying populations in China, Japan, United Kingdom, and