RESEARCH ADVANCES

DNA Data Density: 70 Billion Books in 55,000 Oligos!

Barry E. DiGregorio

DNA provides a capacious medium for storing digital information at densities much higher than those being used in the computer industry, according to George Church and Sriam Kosuri of Harvard Medical School and the Wyss Institute for Biologically Inspired Engineering, both in Boston, Mass., and their collaborators at John Hopkins University in Baltimore, Md. This approach to harnessing DNA for such storage might be ready for practical use within a decade, they say. Details appear online August 16, 2012 Science (doi: 10.1126/science.1226355).

In proof-of-principle experiments, the researchers encoded and read a 5.27-megabit book using next-generation DNA synthesis and sequencing, according to Kosuri. This feat amounts to converting an html-coded draft of a 53,426-word book into a 5.27-megabit bitstream and then recasting 70 billion copies of that draft onto nearly 55,000 oligonucleotides, containing 96-bit data blocks amid 159 nucleotides. The information is split into “addressed data blocks” to eliminate a need for long DNA constructs that would be difficult to assemble. This approach condenses 1,000 times more data per unit than previously could be stored within DNA, he says. “The advantages of density, longevity, and future readability are all strongly in favor of DNA.”

The practical holdups are speed of writing and reading and cost, which needs to drop approximately 1 million-fold to be competitive with current technologies, Kosuri continues. “Over the last 10 years we have achieved that level of price drop already, the question is how quickly the sequencing and synthesis prices continue to drop. At its current pace, we think about a decade.”

Reading data stored in DNA molecules depends on DNA sequencing technology, which is in flux and advancing at breakneck speed, according to Kosuri. “There are plans for new sequencing technologies that will . . . allow sequencing without any amplification, directly placing the DNA on the key,” he says.

How much DNA is required to save data now being generated? By some estimates, the total output of data in 2011 was about 1.8 zettabytes, and that volume is expected to grow to 50 zettabytes by 2015, according to Kosuri. “We estimate using our technology, that this would be a few kilograms of DNA, which is a lot,” he says. “You couldn’t really store that as one big hunk, but stored in a 1,536-well plate, it’s about 1,000 of those plates.”

“The article represents a significant breakthrough in the use of applications of DNA for data storage,” says chemist Michael Morris at Trinity College in Dublin, Ireland, referring to the report by Kosuri and his collaborators. “It may be some way from introduction as an everyday technique and use on everyday electronic equipment.” However, magnetic materials have limitations, whereas this may represent a scalable technology for many years and achieve densities much greater than at present. “Of course the time taken to code and decode the information and its use as volatile or read-write memory applications is limited. It is more likely to find application for permanent storage and may hold very significant
promise for large volume storage in libraries.”

Bary E. DiGregorio is a freelance writer in Middleport, N.Y.

RESEARCH ADVANCES
Harnessing Cytokine-Triggered Response Might Enhance Vaccines

Carol Potera

Cytokines, not antigens, launch T cells against invasive microbial pathogens, and only later do the refinements of antigen recognition come into play, according to Gregoire Lauvau and his collaborators at the Albert Einstein College of Medicine of Yeshiva University in New York, N.Y. Thus, they challenge the long-held dogma that the host response to infection begins with memory T cells being activated when they recognize antigens on pathogens.


“Many different classes of pathogens induce a strong inflammation and then activate a pattern of secreted cytokines that are strikingly conserved,” Lauvau says. “Our study demonstrates that specificity is there, but it is given by specific pathways of activation and secreted cytokines and not cognate antigen as one would think, and one cell type does it most efficiently—namely, the inflammatory monocytes.” Moreover, he adds, “cytokines IL18 and IL15 . . . are sufficient to induce a program of differentiation . . . with no need of cognate antigen. To my knowledge no other studies have documented this.”

Inflammatory monocytes orchestrate this fast-acting host immune response after exposure to a variety of microbial pathogens, including *Listeria monocytogenes*, cytomegalovirus, *Streptococcus pneumoniae*, and the parasite *Plasmodium berghei*. For example, when mice are infected with any one of these pathogens, blood-borne inflammatory monocytes, designated ly6C+ CCR2+, rapidly produce interleukin-15 (IL-15) and interleukin-18 (IL-18). These cytokines contribute to innate immune defenses even in the absence of specific antigens, according to Lauvau. “You do need the antigen later on to cause memory T cells to multiply and get full pathogen-specific protection,” he says.

CCR2+ is a chemotaxis receptor that controls the rapid release of these monocytes from bone marrow when the host immune system mounts an inflammatory response. Human CCR2+ monocytes that express CD14 are equivalent to mouse ly6C+ CCR2+ inflammatory monocytes, according to Lauvau. “An equivalent event may occur in humans, but it’s probably more complicated,” he says. The human counterpart awaits analysis.

Vaccines typically incorporate pathogen-derived antigens that can induce memory T cells in the host that later recognize invading pathogens on the basis of those antigens. However, several weeks may elapse after an individual is vaccinated before his or her immune system is protected against infection. These findings suggest there may be a way to overcome that lag, by harnessing this alternate, faster response against bacteria, viruses, and parasites, Lauvau says. “It’s too early to apply these findings clinically. We still need to identify all the cells and signaling molecules that are involved, and learn how and when the immune system switches from the first phase of protection to the second phase where you have an antigen.”

“The study spearheaded by Lauvau provides much-needed mechanistic insights on the early stages of immune activation,” says Amariliz Rivera at the University of Medicine & Dentistry of New Jersey in Newark. “Moreover, the findings provide the basis for developing novel therapeutics targeting inflammatory monocytes and/or IL-15 and IL-18 to boost immunity.”

Carol Potera is a freelance writer in Great Falls, Mont.

MINITOPIC
Viruses Emerge, While Another Is “Retired” from Fatigue Syndrome

Sharp-eyed analysts continue to detect and identify novel disease-associated viruses or, less often, rule them out for causing perplexing syndromes. Recent examples include:

• Last September, public health authorities reported two cases of SARS-like infections attributed to a novel coronavirus that apparently originated in the Middle East. However, the virus does not seem to be transmitted from one human to another and, through the middle of October, no additional cases were detected, according to officials of the World Health Organization. To learn more about the virus, see the October 17, 2012 *New England Journal of Medicine* (doi: 10.1056/NEJMoa1211721).

• The recently isolated and analyzed Bas-Congo virus is implicated in three human cases, two of them fatal, of acute hemorrhagic fever in 2009 in the Democratic Republic of Congo. It is unlike the Ebola or Lassa viruses but is more closely related to rabies virus, according to Eric Leroy of the Centre International de Recherches Médicales de Franceville in Gabon, Africa, and his collaborators. Details appear in the September 27, 2012 *PLOS Pathogens* (http://dx.plos.org/10.1371/journal.ppat.1002924).

• The mouse retrovirus called XMRV (xenotropic murine leukemia-related virus), a candidate for causing chronic fatigue syndrome (CFS), is now being ruled out as responsible for CFS after rigorous comparisons between 147 individuals with this syndrome and another 146 matched individuals who do not have CFS, according to W. Ian Lipkin of the Mailman School of Public Health of Columbia University in New York, N.Y., and his collaborators. Details appear in the September-October 2012 *mBio* (doi:10.1128/mBio.00266–12).
MINITOPIC
Research Findings Tie Microbiota to Various Diseases

Researchers are continuing to investigate how the microbiota might be linked to a variety of diseases. Recent findings include:

- High levels of antibodies to Porphyromonas gingivalis, a pathogen from the oral cavity, correlate with a twofold elevated risk for pancreatic cancer, while high antibodies for commensal bacteria from that site are linked with a 45% lower risk, according to Dominique Michaud of Brown University in Providence, R.I., and her collaborators. Details appear in the September 18, 2012 Gut.
- Microorganisms in the lungs of individuals with cystic fibrosis have a distinct “signature,” including reduced diversity, compared to those who do not have this disease, according to David Comfeld of Stanford University Medical School in Stanford, Calif., and his collaborators. Details appear in the September 26, 2012 Science Translational Medicine.
- A relatively high level of opportunistic pathogens, a decrease in butyrate-producing bacteria, and enrichments of microbial functions conferring sulfate reduction and oxidative stress resistance among bacteria of the gastrointestinal tract are linked to one’s risk of developing type 2 diabetes, according to Jun Wang and Kirsten Kristiansen from the University of Copenhagen in Copenhagen, Denmark, and their collaborators. Details appear in the September 26, 2012 Nature doi: 10.1038/nature11450.
- In driving inflammatory responses, the gut microbiota can promote the development of colorectal cancer in mice, according to Christian Jobin of the University of North Carolina at Chapel Hill and his collaborators. Details appear in the October 5, 2012 Science DOI: 10.1126/science.1224820.

RESEARCH ADVANCES
Combatting Drug-Resistant Fungi

Shannon Weiman
The molecular chaperone Hsp90 is what appears to be the Achilles’ heel of fungal pathogens—a target that, once inhibited, helps to avoid or overcome resistance to other antifungal drugs, according to Leah Cowen of the University of Toronto in Toronto, Ontario, Canada. However, because similar chaperone proteins are found in mammals, this approach will need some fine-tuning to avoid toxicities, she points out. Cowen spoke during the symposium, “New Approaches in the Treatment of Fungal Infections,” convened as part of the 2012 ICAAC, held in San Francisco last September.

Hsp90, which helps proteins to fold and function properly, including when subject to drug-induced stress, interacts with many fungal proteins. Among them, calcineurin, a calcium-activated phosphatase, is particularly critical, according to Cowen. “Hsp90 physically interacts with the catalytic subunit of calcineurin, maintaining it in stable conformation that is poised for activation,” she says. When activated, calcineurin dephosphorylates transcription factors such as Crz1, allowing them to translocate to the nucleus and activate gene expression programs that enhance fungal survival.

Inhibiting Hsp90 proves potent when combined with conventional antifungal drugs, she continues. “Azoles are fungistatic against C. albicans and inhibit growth but do not eradicate fungal burden, creating conditions that favor the emergence of drug resistance. In combination with Hsp90 inhibition, fungistatic azoles become fungicidal.”

Such Hsp90 inhibitors prevent fungi from developing resistance in vitro and, even more strikingly, restore drug susceptibility in drug-resistant clinical isolates. Hsp90 inhibitors are also effective in the context of biofilms, in which fungal pathogens are particularly resistant to treatment. In vivo, pharmacological inhibition or genetic manipulation of Hsp90 attenuates fungal virulence, rescuing animal hosts from lethal doses of drug-resistant fungi. These findings hold true for di-

Micrograph of Candida albicans cells. C. albicans is among the fungal pathogens that are developing resistance to antifungal agents, complicating their treatment in human infections. Researchers have targeted the molecular chaperone Hsp90 as a means of preventing or overcoming resistance in fungal pathogens. (Photo © iStockphoto/Karl Dolenc.)
verse classes of fungi, including the yeast *Candida albicans* and mold *Aspergillus fumigatus*, in the face of several classes of antifungal drugs, including azoles and echinochidans.

Hsp90 inhibitors are well tolerated in humans and are currently in clinical trials as antineoplastic agents. However, in mice these drugs have detrimental effects in the context of infection by nonselectively inhibiting mammalian Hsp90, which impairs immune response. Cowen and her colleagues are in the process of screening for fungal-selective inhibitors, and have identified some leads that may be applicable in the clinical setting.

Alternatively, Cowen suggests targeting the downstream effector calcineurin. Calcineurin is regulated by KDACs, which deacetylate key lysine residues to enable functional conformation. Cowen has found that inhibiting KDACs is just as effective as inhibiting Hsp90 itself in both in vitro and in vivo studies examining antifungal drug resistance, biofilms, and host survival. KDAC inhibitors are approved for use in humans against leukemia and are in clinical trials for the treatment of other cancers; however, here too it will be important to identify fungal-selective agents. “The divergence of KDACs between fungi and humans is far greater than that for Hsp90, suggesting this might provide a more attractive strategy for antifungal therapy,” says Cowen.

“Ideally, a new therapeutic strategy for fungal infectious disease would enhance the efficacy of existing antifungal drugs, block the emergence of drug resistance, have fungicidal activity, and demonstrate broad efficacy against diverse fungal pathogens. We have established that harnessing fungal Hsp90 meets all of these criteria and has profound therapeutic benefits,” Cowen concludes.

**RESEARCH ADVANCES**

**Next-Generation Sequencing Provides Help in Growing “Uncultivable” Microbes**

**John Otrompke**

Faster methods of sequencing microbial genomes might hold a key to understanding those microbes well enough to culture some isolates that are considered among the most intractable, according to Joerg Graf of the University of Connecticut in Storrs and his collaborators. He spoke during the 2012 International Symposium on Microbial Ecology (ISME), which convened last August in Copenhagen, Denmark.

“Sometimes these ‘unculturable’ microbes are in an inactive state, just hanging out in an environment, and some kind of signal has to revive them,” Graf says. “Other times, they require specific nutrients to allow them to proliferate.”

Graf applied this approach to the first-time culturing of an as-yet-unnamed microbe that is related to *Rikenella*, bacteria that are found in the digestive tracts of numerous animal species. “We had an organism we couldn’t cultivate, so we used 454 sequencing to see what the organism was like inside the host animal, and then could supply the nutrients it needed to grow,” he says, referring to a commercially available DNA sequencing procedure. The host for the *Rikenella*-like microbe is *Hirudo verbana*, a leech that is used in medicine, including to treat tissue grafts.

Metatranscriptomes reveal which genes in the microorganisms are highly expressed at a specific time, pointing to some of its critical nutritional preferences, according to Graf and his collaborators, some of whose earlier findings appear in the April 2011 *mBio* (doi: 10.1128/mBio.00012-11). During the 2012 ISME, he described how they are using 454 pyrosequencing to profile the microbial community within the leech gut. “Initially, we were thinking that the bacteria proliferated on something supplied in the leech’s blood meal,” he says. Instead, the *Rikenella*-like bacteria grow on host-provided mucin.

“Another reason this procedure can be challenging is because most RNA in bacterial cells is ribosomal RNA, which can be very challenging to remove,” Graf continues. “We could sequence 98% of it, but it does not really tell us what the physiology of the unculturable microorganism is like. But with this next-generation technique, we can just sequence through, because we can still sequence the messenger RNA, even though a lot of ribosomal RNA is left in the sample.”

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“This research is significant in several ways,” says Angela Douglas of Cornell University in Ithaca, N.Y., who uses similar technologies to study microorganisms that associate with insects. “The 1980s saw a dramatic revolution in microbiology, when people showed you could identify a microorganism by its RNA without culturing it. We learned of a biodiversity we hadn’t imagined, and of two different classifications of microorganisms, the bacteria and archaea. It also led to the discovery of enormous viruses with very large genomes. It seems we’ve gone from the viewpoint that if we can’t culture it, we can’t study it, to the viewpoint where sequencing analysis almost replaces culturing, and now we’ve come full circle to where sequencing data can enhance our potential to culture an organism.”

John Otrompke is a writer based in Chicago, Ill.

**RESEARCH ADVANCES**

**Laccase and Iodide Salts May Protect Wood against Molds**

**David C. Holzman**

Incubating wood with iodide salts and the oxidizing enzyme, laccase, yields a
surface that resists attack by molds and other wood-destroying microbes, according to Mark Schubert of Swiss Federal Laboratories for Materials Science and Technology in St. Gallen, Switzerland, and his collaborators. Details appear in the October 2012 *Applied and Environmental Microbiology* (78: 7267–7275).

The logic behind the pairing of these ingredients to help in protecting wood against microorganisms is simple, according to Schubert. Iodine has antimicrobial properties on its own. Moreover, published reports suggest that the enzyme laccase can transform unreactive iodide to its active iodine form, he says. “Reactive iodine binds to the lignin in wood.” Indeed, when these two agents are combined to treat wood, it shows “high resistance against colonization by five different classes of heterotrophic microorganisms, even after intensive leaching of the treated wood.”

“Unlike conventional wood preservatives, which are only suited for outdoor applications, our method could also be interesting for indoor applications with high demands for hygiene, such as in hospitals, for kitchens, and for treating pianos,” Schubert says. “We believe this is an environmentally friendly alternative to current wood preservatives, which mostly contain highly toxic compounds such as arsenic, copper, and chromium.”

The cost of laccase should prove competitive, thanks to large-scale fermentation, and the use of waste materials to produce this enzyme, according to Schubert and his collaborators. The enzyme, a copper-containing oxidizing enzyme, was first recognized during the latter part of the 19th century. It is found in many types of plants and fungi.

Olaf Schmidt at the University of Hamburg in Hamburg, Germany, and a fellow of the International Academy of Wood Science, is skeptical that this approach to preserving wood will prove practical. One reason behind that skepticism is that the technique was tested with specimens of only one type of wood, namely spruce, and only very small samples were evaluated, he says.

Additionally, the treated wood specimens were not subjected to harsh enough treatments, according to Schmidt. The microorganisms that typically prove the most damaging for wood—namely, molds and soft-rot fungi—were not included in the tests, he says. Moreover, because the laccase-iodine treatment affects only the surface, the underlying wood is likely to be vulnerable to molds. Wood staining fungi “grow deeper into the woody tissue,” he adds. “All surface protection techniques will be insufficient,” particularly where wood comes into...
contact with soil and water, which is the principal “habitat for soft-rot fungi!” he says. Protecting wood against such microorganisms requires treating them under pressure with salts or with creosote oils. “In the current state the proposed technique is a pure laboratory method, and I have doubts with respect to any future practical application,” he says.

Schubert says that the technique was tested successfully against blue stain and wood decay fungi, which grow into the wood. Laccase iodination “creates covalent chemical bonds between the wood structure and iodine, which are highly resistant to leaching during outdoor use,” he adds. Moreover, laccase iodination can be conducted under pressure, thus impregnating the wood well below the surface.

David C. Holzman is the Microbe Journal Highlights Editor

RESEARCH ADVANCES

Two-Target DNA Inhibitors among New Drug Prospects

Jeffrey L. Fox

Much of the recent innovative work in antibacterials was aimed at inhibiting DNA gyrase and topoisomerase, the same targets as quinolone antibiotics, judging from the poster summary session, “Early New Antimicrobial Agents,” convened as part of the 2012 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), held in San Francisco, Calif., last September. Other hopefuls include improved conventional quinolones, polypeptides that target DNA across a range of bacterial pathogens, a targeted prospect to treat tuberculosis patients, new β-lactamase inhibitors to augment β-lactam antibiotics, a new approach to curbing colistin’s harmful effects, and improved candidates in the relatively new family of echinocandin anti-fungal drugs.

Dual-targeting inhibitors of DNA gyrase/topoisomerase IV belong to a “new class of broad-spectrum” antibacterials that are “cidal,” meaning they kill bacterial pathogens, according to John Finn of Trius Therapeutics in San Diego, Calif. These “pyrimidinoindole” compounds are “sisters” to fluoroquinolones, albeit siblings with a 50-year age gap and no synergy in terms of antibacterial activities, he says. However, the pyrimidinoindoles provide coverage against almost “all known strains” that are resistant to fluoroquinolones, and they show activity and efficacy against a variety of bacterial pathogens in “multiple models” of infectious diseases when tested in rodents.

Similarly, the 2-pyridone EV-035 and other analogues in this class are also bactericidal topoisomerase and gyrase inhibitors of bacterial pathogens, according to Jutta Heim of Evolva in Reinach, Switzerland. The current lead compound, GC-072, inhibits both these enzymes from _Escherichia coli_, but is inactive against the topoisomerase from humans, she says. It has “very striking” activity against many pathogens, including a “very nasty panel of multidrug resistant strains.” Moreover, she adds, “It is not so easy to raise resistance to these 2-pyridones.”

KPI-10 is an “improved fluoroquinolone” that can be orally or intravenously administered and which has broad-spectrum activity against aerobic bacterial pathogens, according to James Ge of Kalidex Pharmaceuticals in Menlo Park, Calif. Notably, KPI-10 is more active than other fluoroquinolones against _E. coli_, and it also shows “excellent activity” against _Neisseria gonorrhoeae_, he says. Separately, DS-8587 is another new fluoroquinolone with broad-spectrum activity against both gram-negative and gram-positive bacterial pathogens, with activity against many anaerobic pathogens, according to Kazuki Hoshino of Daiichi Sankyo in Tokyo, Japan.

PT3.33 belongs to a very different set of antibacterial agents, according to Heather Fairhead of Phico Therapeutics in Cambridge, U.K. It encapsulates a gene encoding small acid-soluble spore proteins (SASPs) into a nanoscale-delivery vehicle (NDV) that can target specific strains of gram-negative bacterial pathogens. The “pyrimidoindoles” are “sisters” to fluoroquinolones, albeit siblings with a 50-year age gap and no synergy in terms of antibacterial activities, he says. However, the pyrimidinoindoles provide coverage against almost “all known strains” that are resistant to fluoroquinolones, and they show activity and efficacy against a variety of bacterial pathogens in “multiple models” of infectious diseases when tested in rodents.

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bacterial pathogens. Those proteins bind to DNA, changing its conformation and making it more rigid—inactivating it and thereby killing cells into which it is introduced, she says. Because the SASPs “can’t get into cells on their own,” the strategy is to combine genes encoding them with delivery vehicles that confer specificity against pathogens while sparing commensal bacteria, she adds. Although the NDVs target bacteriophage receptors, there is a “strategy to overcome phage resistance mechanisms,” she notes, also pointing out that the SASPs do not depend on specific sequences when they bind to DNA molecules.

Unlike the foregoing broad-spectrum agents being developed, TBA-354 is a narrow-spectrum, “new generation” nitroimidazole with potent bactericidal activity against both replicating and nonreplicating Mycobacterium tuberculosis and is active against many drug-resistant strains of this pathogen, according to Zhenkun Ma of the Global Alliance for TB Drug Development in New York, N.Y. Although the compound is active under both aerobic and anaerobic conditions, the mode of action is “not fully understood” and may include “two modes” to account for its action under these different conditions, he says.

Not antibacterial on its own, RPX7009 is the lead compound from a new class of serine carbapenemase inhibitors, according to Michael Dudley of Rempex Pharmaceuticals in San Diego, Calif. It is a “very efficient inhibitor” and shows “progressive, irreversible binding” when tested against carbapenemases, he says. When used with carbapenems against bacterial strains, including a panel of multidrug-resistant gram-negative bacterial pathogens, RPX7009 can “drive down their MICs [minimal inhibitory concentrations]” for this class of \(\beta\)-lactam antibiotics.

Dextrin conjugates of colistin provide a means for reducing the toxicity of this venerable cyclic polypeptide antibiotic, whose ill effects on kidneys help to discourage its clinical use, according to Elaine Ferguson of the University of Cardiff in Cardiff, U.K. By attaching dextrin polysaccharides, however, colistin can be kept from entering a patient’s kidneys but still travel via the blood to sites of infection, she says. Moreover, the dextrin helps to protect colistin against proteases, while adding amylases can liberate the antibacterial cyclic polypeptide from the conjugate in, for instance, “wound environments.”

Finally among the antimicrobial candidates highlighted during the 2012 ICAAC poster session—in this case, an antifungal agent—is ASP9726, a “next-generation echinocandin” with enhanced activity over older members of this class against several fungal pathogens, including Aspergillus fumigatus and Candida spp., according to Souichirou Akamatsu of Astellas Pharma in Tsukuba, Japan. This candidate drug also performs well in treating fungal infections in several animal models of disease, including those involving mice, rabbits, and guinea pigs, he says.