

Technology Review 100

Meet the world's top young innovators. From computing to biomedicine to nanotech, their technologies will transform our lives.

INNOVATION HAS BECOME an endeavor without borders. And nowhere is that more evident than in this year's TR100—*Technology Review*'s selection of 100 top innovators under 35—a group that demonstrates that the barriers to innovation, both geographical and disciplinary, are crumbling. The TR100 for 2004, the fourth year that *Technology Review* has named its list of innovators, hail from places as varied as Singapore, Boston, South Korea, Israel, China, and India—and many are developing technologies that defy easy classification, often fusing recent advances in computing, medicine, and nanotech. On the list, you'll find leading academic researchers, entrepreneurs, social advocates for technology, and even experts in high-tech entertainment. In short, the TR100 represent the diversity of those using technology to transform the world around us. ■ Choosing the top young innovators is a challenging job—and not something we take lightly. Beginning more than a year ago, *TR* began scouring the world for nominees. As in years past, our editors then relied heavily on an expert panel of judges *(see "TR100 Judges 2004," p. 79)* who carefully whittled down the list, initially more than 600 entries, to the very best and brightest. These are incredibly talented and hardworking people, and in the following 26 pages, you'll read about their achievements and visions. Collectively this group provides an eye-opening picture of the future of technology. On page 76, you'll also read of past TR100 members, many of whom have continued to make world-transforming contributions to technology. ■ Predicting the future of technology is notoriously difficult. But it's a sure bet that the people you'll meet in the following pages will play an important role in shaping it. **—THE EDITORS**

Bio-tech +medicine

Researchers are tearing down the wall between the life sciences and information technology

BY ERIKA JONIETZ PHOTOGRAPH BY FREDRIK BRODEN

BIOLOGISTS AND PHYSICIANS are notorious for cyberphobia, but this year's TR100 honorees in biotechnology and medicine are erasing that stereotype—and the boundaries between the life sciences and information technology along with it. Many are pioneering fields intimately connected with or influenced by computing, areas as diverse as bioinformatics and brain-computer interfaces. Some of the most exciting advances are happening in electronic health care, synthetic biology, and ultrasensitive diagnostics. ■ With the addition of computers, "I see the whole medical process being very different—much less haphazard, much more rational," says **Colin Hill**, founder of Gene Network Sciences, which uses computer models of cells to predict how well potential drugs will work. "Ultimately, I see this future world of medicine where doctors can measure molecular activity in the body, feed it into a computer model, and determine the right treatment for the person." ■ Even before that day arrives, mobile computing will change the nature of medical practice, says **Vikram Kumar**, a resident at Boston's Brigham and Women's Hospital. He believes that simple, portable computer programs can encourage people to adhere to treatment regimens—one of the biggest challenges in medicine today. As a medical student, Kumar started a company called Dimagi to develop such tools. One example is a PDA-based game that helps diabetic kids understand how their behavior affects their blood-glucose levels. Kumar hopes that one day his management systems, combined with cheap, at-home diagnostic

tests that give patients up-to-the-minute data on their physical conditions, will keep people with chronic ailments from landing in the hospital. "The biggest dream I have is that one day we can close all the hospitals," he says.

Lauren Meyers could help him empty them out, first. By modeling how people interact in schools, hospitals, and other settings, the University of Texas at Austin mathematician can make detailed predictions about how a disease will spread. She can also use those models to determine which interventions—vaccinating health-care workers or closing schools, for example—will most effectively halt an outbreak. The British Columbia Centre for Disease Control has enlisted her help to create control strategies for future outbreaks of SARS: her models have shown that using masks in hospitals, for instance, should be as effective as more drastic measures such as closing schools.

While researchers like Meyers and Kumar are using computers in a literal sense, others are using ideas borrowed from computing to understand and even "program" living cells. In this new field of synthetic biology, "we're taking existing, well-characterized genes and putting them together in new combinations so that we get interesting behaviors," says Caltech biophysicist **Michael Elowitz**. Synthetic biologists call these new gene combinations "genetic circuits," because they provide a means of rewiring, or programming, a cell's behavior. Ultimately, these researchers hope to program cells to perform crucial tasks. Boston University bioengineer **Tim Gardner**, for instance, wants to program bacteria to develop new antibiotics, clean up the environment, or generate electricity. In each case, he's mapping the genetic pathways that control bacterial metabolism and then trying to manipulate them—to, say, turn toxins into harmless compounds.

Even in cutting-edge medical diagnostics, there are parallels to computing. Electrical engineers have found light to be the nearly perfect medium for transferring data quickly and precisely; similarly, biomedical engineers are using light to obtain information about the body on a finer scale than ever before possible—so that they can detect diseases much earlier and with greater sensitivity.

"The sooner you detect, the better," says **Vadim Backman**, a bioengineer at Northwestern University. Many cancers are curable if doctors detect them early enough, and Backman aims to make sure they do. With his technique, a doctor simply shines light on biological tissue. By collecting and analyzing data about light's wavelength, direction, and polarization as it bounces off different tissues, Backman has developed "fingerprints" of the minute structural changes in cancerous cells. This sensitivity has allowed him to detect colon cancer in rats earlier than with any other method; human tests have already begun. By inserting a probe only 1.5 millimeters wide just a few centimeters into a patient's rectum, a doctor should be able to predict whether the patient has precancers in any part of the colon. Backman hopes this will provide a cheap, quick, and easy screen for colorectal cancer.

Vasilis Ntziachristos at Harvard Medical School has similar goals. He has developed the hardware and software needed to produce 3-D images that reveal the locations of telltale molecules, such as cancer-related proteins, deep inside the body. Monitoring such molecules could allow physicians to make earlier and more precise diagnoses than they can by examining the anatomical features detected by imaging techniques such as CT and MRI scans. Today, the technology, which is similar to a CT scan but uses fluorescent tags and beams of infrared and visible light instead of radioactive dyes and x-rays, is used to observe molecules at work in living animals, helping researchers decipher how cells normally function and what goes wrong in disease. Within a few years, doctors may be able to use such molecular-imaging tools to detect tumors smaller than one millimeter in size.

These researchers don't think small, and some of their goals may take decades to reach. Yet within our lifetimes, says Kumar, electronic health care, synthetic biology, ultrasensitive diagnostics, and other technologies will combine to create a whole new way of practicing medicine, allowing doctors to personalize treatments and even prevent illnesses before they strike. Hill agrees. "It's going to be profound, more so than a lot of the discoveries that happened in the physical sciences and computing sciences," he says. "Science is finally about life now; it's finally about us." TR

TR100 STARTUPS IN BIOTECH + MEDICINE

INNOVATOR	COMPANY FOUNDED/COFOUNDED	TECHNOLOGY/MILESTONES
Ryan Egeland	Oxamer (Oxford, England)	Supercheap DNA chips for research and diagnostics; produced using proprietary electrochemistry
Tim Gardner	Cellicon Biotechnologies (Boston, MA)	Precise mapping of bacterial gene pathways to discover novel antibiotics for treating resistant infections
Colin Hill	Gene Network Sciences (Ithaca, NY)	Predictive modeling of cells to speed drug discovery; raised about $9 million
Shana Kelley	GeneOhm Sciences (San Diego, CA)	Molecular diagnostics using electrochemical detection of DNA and RNA; plans to introduce first products in 2004
Gloria Kolb	Fossa Medical (Needham, MA)	Devices to treat the urinary and biliary tracts; four have received U.S. Food and Drug Administration approval
Vikram Kumar	Dimagi (Boston, MA)	Computer tools to help patients and health-care providers; PDA tools in use in India and South Africa
David Liu	Ensemble Discovery (Cambridge, MA)	Using DNA to direct the synthesis of drugs and other chemicals; raised $15 million in its first venture round
Ananth Natarajan	Infinite Biomedical Technologies (Baltimore, MD)	Neurology, cardiology, and gynecology devices; two in clinical trials; raised $9.5 million in government funding
Sandra Waugh Ruggles	Catalyst BioSciences (South San Francisco, CA)	Designing protein-cutting enzymes to treat cancer and inflammation; recently closed first venture round

YAAKOV BENENSON

Age: 28 | Graduate student | Weizmann Institute of Science

Yaakov Benenson wants to shrink your doctor. Or more accurately, he wants to replace physicians with molecular machines that diagnose and treat diseases with phenomenal precision, each what he calls a "doctor in a cell." ■ In just five years, Benenson has taken the concept from drawing board to test-tube prototype. Working at the Weizmann Institute of Science in Rehovot, Israel, he has built molecular devices—essentially DNA strands and enzymes—able to analyze genetic changes associated with lung and prostate cancers and to release a drug in response. These prototypes are "a beautiful work of molecular and conceptual integration, pointing the way toward truly integrating diagnostics with therapeutics," says George Church, director of the Center for Computational Genetics at Harvard Medical School. ■ "Using these tiny diagnostic machines, we could selectively treat only the diseased cells," Benenson says. For example, the prototype device for small-cell lung cancer assesses the activity of four genes. Cancerous cells produce extra RNA copies of each of these genes. Consecutive sections of the DNA strand in the prototype bind, in turn, to these RNA strands; when they do, an enzyme chops them off. If all of the cuts are made properly, the enzyme releases and activates an anticancer drug that has been tethered to the DNA in an inactive form. ■ Benenson's molecular machines offer a unique combination of precision and flexibility. A single one of them can be designed to look for up to 10 different diagnostic markers before it releases its drug payload. The devices can also be tailored to several different diseases through simple-to-make changes in their DNA sequences. ■ These machines represent a quantum leap not only in medicine but also in DNA computing. Benenson's molecular "doctors"—which are computers in the sense that they store information and analyze it following a yes/no logic—are "directed at a practical interface with biomedicine rather than losing an abstract race with existing computers on their own turf," says Church. ■ It will be a while before molecular machines replace existing systems of diagnosis and treatment: Benenson estimates three or four years before even simple versions that work in a living cell are ready, and perhaps decades before they can be tried in people. If the DNA doctors prove as successful in the body as they have in the lab, though, they might spark a revolution in medicine.

VADIM BACKMAN
Age: 31
Assistant professor, Northwestern University
Found a way to spot colon cancer earlier than was previously possible—and well before it has spread—by measuring the changes that occur when white light interacts with tumor cells.

SELENA CHAN
Age: 31
Research scientist, Intel
Designs nanotechnological tools to detect viruses, bacteria, and, for the first time, single molecules of DNA in medical samples.

REBEKAH DREZEK
Age: 30
Assistant professor, Rice University
Develops photonic technologies that use targeted nanomaterials to detect, monitor, and treat breast and gynecologic cancers painlessly, and at a fraction of the cost of conventional approaches.

RYAN EGELAND
Age: 29
Director and cofounder, Oxamer
Slashed the cost of producing a DNA chip from hundreds of dollars to a few dollars by combining microfluidics, computer control, and novel electrochemistry. Cofounded Oxford, England's Oxamer with genetic-analysis pioneer Edwin M. Southern to commercialize the technology.

MICHAEL ELOWITZ
Age: 34
Assistant professor, Caltech
Combines existing genes to build artificial biological pathways, or "circuits," that operate inside cells. The goal: better understanding how cellular behavior is naturally controlled—and how it might be reprogrammed.

TIM GARDNER
Age: 31
Assistant professor, Boston University
Constructs computer models of cellular pathways in order to optimize bacteria for energy production and environmental remediation. Cofounded Cellicon Biotechnologies in Boston, MA; the company uses the cellular models to improve antibiotics.

SHANA KELLEY
Age: 34
Assistant professor, Boston College
Builds nanoscale electrochemical and electrical sensors to detect medically relevant gene sequences and proteins. Cofounded San Diego, CA's GeneOhm Sciences to produce molecular diagnostics based on one such technology.

GLORIA KOLB
Age: 32
Founder and president, Fossa Medical
Devised a way to remove kidney stones more cost effectively and less invasively by taking advantage of the ureter's tendency to dilate around foreign objects. Her Boston-based company has two devices on the market.

VIKRAM SHEEL KUMAR
Age: 28
Cofounder and CEO, Dimagi
Founded Dimagi in Boston to develop interactive software that motivates patients to manage chronic diseases such as diabetes and AIDS. His PDA-based systems are being used in rural India and South Africa.

JÖRG LAHANN
Age: 33
Assistant professor, University of Michigan
Designed an electrically switchable surface coating that can alternate between attracting and repelling water. Such "smart surfaces" could coat biomedical implants for use in tissue engineering, sensing, or drug delivery.

ERIC C. LEUTHARDT
Age: 31
Resident physician, Washington University School of Medicine
Showed that a patient could achieve real-time control of a computer via electrodes placed on the brain's surface. Such an interface could allow paralyzed people to communicate and, eventually, control prostheses.

DAVID LIU
Age: 31
Associate professor, Harvard University
Applies evolutionary principles to synthetic molecules by linking starting materials to DNA strands; the strands' sequences determine which of them bind to each other, and thereby direct reactions between the starting materials.

FRANK LYKO
Age: 34
Group leader, German Cancer Research Center
Aims to reprogram cancer cells to be more like normal cells by developing compounds that block the aberrant modification of DNA in cancer cells.

LAUREN MEYERS
Age: 31
Assistant professor, University of Texas at Austin
Helped public-health officials control epidemics of walking pneumonia and SARS with sophisticated mathematical models that predict how a disease will spread through networks of human interactions.

ANANTH NATARAJAN
Age: 33
CEO, Infinite Biomedical Technologies
Cofounded his Baltimore, MD, firm to bridge the gap between research and patient care. One of its technologies will enable implantable cardiac devices to detect incipient heart attacks.

VASILIS NTZIACHRISTOS
Age: 34
Assistant professor, Harvard University
Facilitated noninvasive optical imaging of proteins and other molecules in the body—which could lead to ultraprecise diagnosis of cancer and other diseases—through his theories, software, and instruments.

SHAYN PEIRCE
Age: 29
Assistant professor, University of Virginia
Models how individual cells in tissues migrate, multiply, and develop during processes such as blood vessel growth. The models should aid tissue engineering and drug development.

COLIN HILL
Age: 32 | Cofounder and CEO | Gene Network Sciences

Four out of five drugs fail in human trials. But Colin Hill says that at his Ithaca, NY, startup, "We think we are the answer." The physicist turned entrepreneur aims to more than double human trials' success rate by virtually prescreening drugs in computer models of human cells. His company uses these "virtual cells" to uncover how the compounds work and predict which ones will fare best in human tests. Drugmakers share his enthusiasm: his company has deals with two of the top five drug firms.

NATAN DVIR/GETTY IMAGES (BENENSON)

SANDRA WAUGH RUGGLES
Age: 30
Cofounder and scientist, Catalyst Biosciences
Uses clever testing schemes to determine which protein-slicing enzymes make the cut as potential drugs. Her South San Francisco company is developing the protease-based treatments for cancer and inflammation.

CHRISTOPH SCHAFFRATH
Age: 33
Business development manager, Onyx Scientific
Discovered, as a grad student, an enzyme that could enable environmentally benign production of fluorine-containing compounds such as Teflon and Prozac, which are now made via noxious chemical processes.

MONISHA SCOTT
Age: 33
Director, Target Discovery and Validation, Inimex Pharmaceuticals
Determined how small, natural proteins boost the immune response. Inimex, in Vancouver, British Columbia, develops synthetic versions of the proteins for antibiotic-resistant infections.

CHRISTINA SMOLKE
Age: 29
Assistant professor, Caltech
Fine-tunes the activity of individual genes via an adaptable technology that is potentially useful in biosensors, gene therapies targeted to specific types of cells, and the development of new antibacterial, antifungal, and anticancer treatments.

KAHP-YANG SUH
Age: 32
Assistant professor, Seoul National University
Came up with the first method that allows researchers to pattern proteins and cells directly onto glass or plastic surfaces or within microfluidic channels without complicated preparation. The technique is potentially a boon not only for basic research but also for the development of chemical and biological sensors.

OLGA TROYANSKAYA
Age: 26
Assistant professor, Princeton University
Devised sophisticated and accurate computer algorithms for analyzing data generated using DNA microarrays. These algorithms allowed her to identify genes involved in a host of diseases, including lymphoma, lung cancer, and gastric cancer.

LEI WANG
Age: 31
Research fellow, University of California, San Diego
Expanded the genetic code in order to allow living cells to incorporate new, unnatural building blocks into the proteins that they make. The technique could one day allow biologists to create new proteins and even entire organisms that have enhanced or novel properties.

SMRUTI VIDWANS
Age: 30 | Postdoctoral fellow | University of California, San Francisco

Tuberculosis kills two million people every year, a tragedy of which Smruti Vidwans was all too aware growing up in India. Resistance to TB drugs is on the rise, and Vidwans thinks the solution may be new drugs that don't kill the bacteria but block the proteins that allow them to reproduce in people. She's launching a company to develop such drugs. It's a huge challenge, but those who know her say she's up to the task.

EMILY NATHAN (VIDWANS); ASIA KEPKA (ZHUANG)

TR100 HONOREES

TR100 JUDGES 2004

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