

spreading HCV to others. Most importantly, more awareness is needed to bring attention to this silent killer—similar to the attention drawn to HIV in the 1980s—to halt the spread of HCV and to develop therapeutics and vaccines to cure those who are infected.

## REFERENCES

- Chisari FV (2005) Unscrambling hepatitis C virus–host interactions. *Nature* **436**: 930–932
- Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M (1989) Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science* **244**: 359–362
- De Francesco R, Migliaccio G (2005) Challenges and successes in developing new therapies for hepatitis C. *Nature* **436**: 953–960
- Feld JJ, Hoofnagle JH (2005) Mechanism of action of interferon and ribavirin in treatment of hepatitis C. *Nature* **436**: 967–972
- Fleckenstein J (2004) Chronic hepatitis C in African Americans and other minority groups. *Curr Gastroenterol Rep* **6**: 66–70
- Hinrichsen H *et al* (2004) Short-term antiviral efficacy of BILN 2061, a hepatitis C virus serine protease inhibitor, in hepatitis C genotype 1 patients. *Gastroenterology* **127**: 1347–1355
- Houghton M, Abrignani S (2005) Prospects for a vaccine against the hepatitis C virus. *Nature* **436**: 961–966
- Laffan G (2005) Dutch government urged to inform public of blood mistakes. *Lancet* **365**: 2165
- Lamarre D *et al* (2003) An NS3 protease inhibitor with antiviral effects in humans infected with hepatitis C virus. *Nature* **426**: 186–189
- Larkin M (2000) WHO's blood-safety initiative: a vain effort? *Lancet* **355**: 1245
- Lindenbach BD *et al* (2005) Complete replication of hepatitis C virus in cell culture. *Science* **309**: 623–626
- Mercer DF *et al* (2001) Hepatitis C virus replication in mice with chimeric human livers. *Nat Med* **7**: 927–933
- Meuleman P, Libbrecht L, De Vos R, de Hemptinne B, Gevaert K, Vandekerckhove J, Roskams T, Leroux-Roels G (2005) Morphological and biochemical characterization of a human liver in a uPA-SCID mouse chimera. *Hepatology* **41**: 847–856
- Reiser M *et al* (2005) Antiviral efficacy of NS3-serine protease inhibitor BILN-2061 in patients with chronic genotype 2 and 3 hepatitis C. *Hepatology* **41**: 823–835
- Shepard CW, Finelli L, Alter MJ (2005) Global epidemiology of hepatitis C virus infection. *Lancet Infect Dis* **5**: 558–567
- Wakita T *et al* (2005) Production of infectious hepatitis C virus in tissue culture from a cloned viral genome. *Nat Med* **11**: 791–796
- WHO (2000) Hepatitis C. [www.who.int/mediacentre/factsheets/fs164/en](http://www.who.int/mediacentre/factsheets/fs164/en)
- Zhong J, Gastaminza P, Cheng G, Kapadia S, Kato T, Burton DR, Wieland SF, Uprichard SL, Wakita T, Chisari FV (2005) Robust hepatitis C virus infection *in vitro*. *Proc Natl Acad Sci USA* **102**: 9294–9299

Andrea Rinaldi

doi:10.1038/sj.embor.7400608

# Gambling in the deep sea

The genetic wealth hidden in the deep seas is attracting commercial and academic interest, raising the question whether to regulate bioprospecting in international waters

For decades, the depths of the oceans have fascinated researchers. The discovery of strange creatures perfectly adapted to eternal darkness, high pressure, and other unusual conditions has raised enormous interest in how life emerged on Earth and how it flourishes in such extreme environments (Fig 1). This abundance of life has also lured researchers and biotech companies to the oceans in the hope of finding unknown genes, proteins, and other compounds that could be exploited commercially. Despite the enormous costs that still pose a considerable barrier to deep-sea research and exploitation, some now worry about the negative side effects of deep-sea bioprospecting. Scientists, entrepreneurs, politicians and legal experts have begun to debate problematic issues, such as the preservation of deep-sea biodiversity, habitat protection and sharing of benefits. Their aim is to draft international regulations to prevent environmental and scientific tragedies without hampering discovery.

Scientists have made—and continue to make—exciting discoveries in the depths of the oceans. In the early 1980s, Karl Stetter, a microbiologist from the University of Regensburg, Germany, discovered a hyperthermophilic archaeobacterium that flourishes near submarine vents (Fig 2) at temperatures of about 100 °C (Stetter, 1982). Stetter and his colleagues described another archaeobacterium in 2002, termed *Nanoarchaeum equitans*. This organism is parasitic with an unusually small ribosomal RNA and now represents a new phylum in the bacterial world (Waters *et al*, 2003; Huber *et al*, 2002).

The first six months of 2005 saw the publication of the discovery of a jellyfish that uses red fluorescent flashes to lure fish (Haddock *et al*, 2005) and the genome sequence of *Photobacterium profundum* strain SS9 (Vezzi *et al*, 2005), 20 years after the microorganism was isolated from an amphipod animal living 2,500 m deep in the Philippine Sulu Sea (Yayanos, 1995).

Tim Shank, a biologist at Woods Hole Oceanographic Institution (WHOI; Woods Hole, MA, USA), is studying a worm that lives at 80 °C in an oily tar-like pit near submarine vents. The organism lives in the presence of carcinogenic amounts of polyaromatic hydrocarbons, but does not develop cancer. According to Shank, studying the DNA-repair mechanisms of the organism may lead to new insights about cancer growth and even possible treatments.

Shank's research is just one example of the potential commercial possibilities emerging from the genetic wealth in the deep sea, sometimes coined 'blue gold'. Until now, only a few products have made it from research to market. Diversa (San Diego, CA, USA) and New England Biolabs (NEB; Ipswich, MA, USA) sell DNA polymerases isolated from deep-sea vents that offer advantages such as increased thermostability and improved proofreading capabilities for the polymerase chain reaction. Sederma (Le Perray en Yvelines, France) sells Venuceane™, a skin protection product that includes a radical-scavenging enzyme originally discovered in extremophile bacteria from the Gulf of California (Lintner *et al*, 2002). However, the global sales of marine biotechnology products in 2002, including anti-cancer compounds, antibiotics and antivirals, were estimated at about US\$2.4 billion (BCC, 2003).

Such a healthy market for products encourages companies and academics to explore the oceans further for interesting organisms. Diversa, which produces enzymes, proteins and biologically active compounds for pharmaceutical, agricultural and industrial use, maintains an active deep-sea research programme, although it is not the focus of their research, according to Leif Christoffersen, Biodiversity Product Manager at Diversa.

However, the lines between academia and industry are becoming increasingly



**Fig 1** | Tubeworms (*Riftia pachyptila* Jones) found at the bottom of the Pacific Ocean at the East Pacific Rise off the coast of Mexico. These red-blooded animals live of chemosynthetic bacteria near thermal vents on the ocean floor and can grow up to 3 m long. © Woods Hole Oceanographic Institute, Woods Hole, MA, USA.

and the knowledge, and the commercial partners provide funds and other useful capabilities.

Justin Manley, Lead Ocean Engineer at Mitretek Systems, a non-profit scientific research and engineering corporation (Falls Church, VA, USA), explained that alliances between the biotechnology and pharmaceutical sector with other industries, such as the oil and shipwreck salvaging businesses, might become fruitful avenues in the future. “One million dollars is a drop in the bucket compared to what oil companies spend on oil rigs,” he commented. Shank also thinks that as soon as more benefits from deep-sea research materialize, such as new chemicals, proteins and enzymes with new properties, other industries will get into the game. Although the funding is welcome, Shank noted, “We are wary of companies taking the samples and not communicating results...As a result, some academics do not provide samples to industry.”

Past experience shows that this concern is valid. Although researchers discovered the *Thermus aquaticus* microorganism in Yellowstone National Park in 1967, the park does not benefit in any way from sales of the heat-stable Taq polymerase for polymerase chain reactions.

This situation changed with the passage of the Convention on Biological Diversity (CBD) in 1992, which allows governments and organizations to negotiate contracts with scientists when they give them access to national land and water resources. According to Eric Mathur, Vice President of Scientific Affairs and Molecular Diversity at Diversa, before the passage of the CBD, academics had the freedom to patent discoveries and transfer samples to interested industrial partners. The contract between the discoverers of *P. profundum* and the Philippine government, which prohibits any financial gains from discoveries in the Sulu Sea, is an example of how things have changed.

Still, fears remain: environmental groups sued Yellowstone National Park in August 1997 for making the first biodiversity agreement in the USA to share scientific and monetary benefits with Diversa. In a historic decision, a federal court in Washington, DC, approved this agreement between Yellowstone National Park and Diversa on April 12, 2000. In addition, the US National Park Service began conducting environmental analyses to evaluate the

blurred. Stetter, one of the world’s leading experts on extremophilic archaeobacteria, is a co-founder of Diversa. Craig Venter, founder of Celera Genomics, launched the Sorcerer II Expedition in Nova Scotia, Canada, in 2003, to create a genomic catalogue of marine microorganisms. The expedition, now situated off the east coast of Australia, has already shown insights into the diversity and abundance of organisms in samples from the Sargasso Sea near Bermuda (Venter *et al*, 2004). Melanie Wranaker, media contact at the J. Craig Venter Institute (Rockville, MD, USA), said that the research includes the study of extreme environment sites, such as hydrothermal warm seeps, hypersaline lagoons and low-oxygen environments, which may be similar to deep-sea environments and therefore useful for comparative studies. All data collected will be deposited into the public domain for researchers. The Ocean Genome Legacy (OGL) is another

non-profit marine research organization that explores the abundance of life in the deep sea. Their headquarters are located in Ipswich, MA, USA, near NEB, from which the organization receives financial support.

One reason why academic scientists and institutions team up with commercial partners is the high cost of deep-sea research. Few countries can afford dedicated academic deep-sea research programmes and equipment such as specialized ships and submarines (see Fig 3): namely the USA and Japan, although France, the UK and Russia also have deep-sea research capabilities. A 30-day expedition cruise costs roughly US\$1 million, with an average daily operating cost of about US\$30,000. Diversa, which collaborates with Deep Ocean Expeditions, estimate its annual costs to be approximately US\$5–6.5 million to operate the RV Akademik Keldysh ship, owned and operated by the PP Shirshov Institute of Oceanology in Moscow, Russia. These high costs usually require academic and commercial partnerships—academic institutions have the equipment

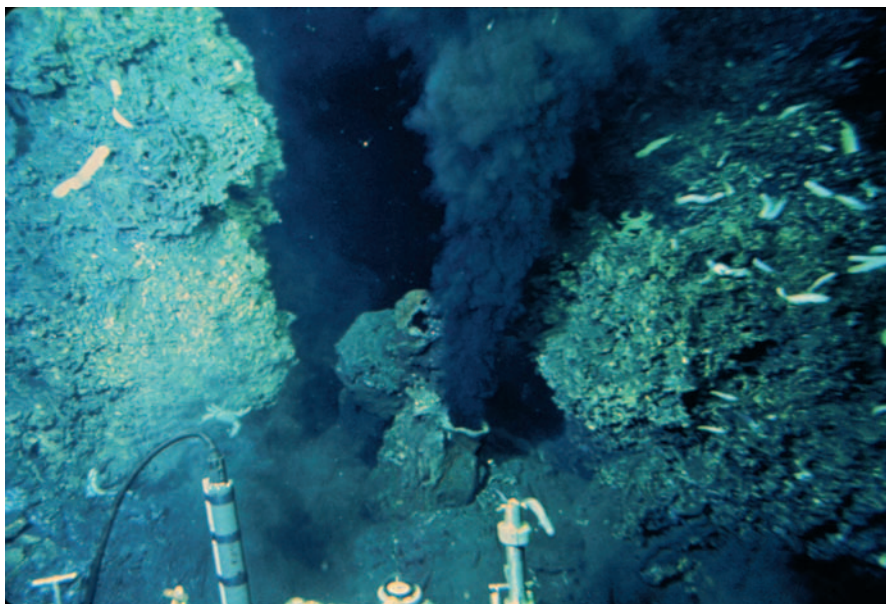
**... a healthy market for products encourages companies and academics to explore the oceans further for interesting organisms**

impacts of bioprospecting benefit-sharing agreements in US national parks. This review may represent the first nationwide study of the environmental impacts of bioprospecting benefit-sharing activities ever undertaken by any country.

Critics also fear that industrial exploitation may create environmental problems similar to overfishing and mining of marine areas. According to Shank, the establishment of thermal-vent marine preserves off the coasts of Oregon and Portugal in the past two years was in part a response to such concerns. However, Barbara Moore, Director of the US National Oceanic and Atmospheric Administration's Undersea Research Program (NOAA; Silver Spring, MD, USA), is less pessimistic about the environmental impact of deep-sea research. She pointed out that the combination of small samples of microorganisms, non-specific sampling techniques and high costs make deep-sea bioprospecting less of a threat to the environment. She added that sea-floor tectonics and 'plumbing' of the vents continually change the environments and their living communities. Moore also stressed that other deep-sea ecosystems, such as cold seeps, methane hydrate seeps and deep-sea corals, also known as cold-water corals, are as important to the overall ecosystem as the deep-sea vents.

### Critics also fear that industrial exploitation may create environmental problems similar to overfishing and mining of marine areas

Although the CBD governs access to genetic resources and benefit sharing between nations and researchers, the maze of regulations for the conservation of biodiversity, sustainability and benefit sharing is complex and cumbersome. Elizabeth Evans-Illidge, a marine scientist at the Australian Institute of Marine Science (Townsville, Qld, Australia), explained that implementing the CBD internationally has been difficult because many countries have not passed domestic laws to address the CBD's objectives. Instead, many rules are based on systems that were in place before the CBD and often do not require benefit sharing.



**Fig 2** | A 'black smoker' on the ocean floor at the East Pacific Rise off the coast of Mexico. The emerging water is 350–400 °C and by mixing with the surrounding cold water causes minerals in the water to fall out, which gives the appearance of black smoke. © Dudley Foster/Woods Hole Oceanographic Institution (Woods Hole, MA, USA).

Consequently, many countries refuse or restrict access to their marine areas. Various countries, including Australia, are therefore working on translating the CBD into national law.

The problem is further hampered by the fact that the open seas—and most of the world's seabed ecosystems—lie in international waters beyond national laws and unregulated by international laws. According to Salvatore Arico of the United Nations Educational, Scientific and Cultural Organization (UNESCO; Paris, France), the UN began to address this problem in 1995 and started to debate international regulations, realizing that the extreme environments of the deep sea would be of academic and commercial interest, similar to the Yellowstone's geysers. Arico commented that the debate then stalled for years owing to a lack of support by some nations that actively conduct deep-sea

... the open seas—and most of the world's seabed ecosystems—lie in international waters beyond national laws and unregulated by international laws

research, most notably the USA and Japan. Eventually, in 2004, Sam Johnston, a member of the UN University Institute for Advanced Studies (UNU-IAS; Yokohama, Japan), commissioned the deep-sea genetic resources report to catalyse further policy development (Arico & Salpin, 2005).

The report, a joint effort between Arico and Charlotte Salpin, a law and policy expert associated with UNU-IAS, makes several key recommendations. First, it emphasizes the need for further study of the "whole world down there—knowing how these ecosystems function is important for the planet", according to Arico. Second, any international regulation should take into account that some deep-sea ecosystems are already threatened by unsustainable use. "While it is impossible to quantify the damage caused by such research on the deep seabed environment, threats include destruction of habitats, unsustainable collection, alteration of local hydrological and environmental conditions, and pollution of various nature," the report states. "The same activities can have very different impacts in various deep sea ecosystems, and cumulative impacts over time..." Third, it should address the problem that at



**Fig 3** | The Alvin submersible, owned and operated by the Woods Hole Oceanographic Institution (Woods Hole, MA, USA).  
© Woods Hole Oceanographic Institution.

present, scientific research in international waters is unregulated. Johnston added that bioprospecting, to be distinguished from pure academic research, has already begun. The absence of international regulations has therefore created negative effects for academic research, most notably secretive scientific protocols, which force each expedition to start *de novo*. He also highlighted the difficulty that governments face when creating regulations for benefit sharing.

The question is whether such international regulations are necessary at all, because of the difficulties of biological research. "Most innovations from marine or any biomaterials require considerable research and so the line between marine scientific research and bioprospecting will be fuzzy," said Dan Distel, Director of the OGL. "It may be very difficult and possibly counterproductive to legally discriminate among research activities based on the intent of the researchers."

Some experts also wonder whether improper language and sensationalizing the problems exacerbate the discussion. Dave Newman of the National Cancer Institute's Developmental Therapeutics Program (Bethesda, MD, USA), commented

### DEEP-SEA RESEARCH TECHNOLOGY

Innovations and improvements to existing deep-sea expedition technology may help lower the cost of deep-sea research in the near future. Justin Manley, Lead Ocean Engineer at Mitretek Systems, pointed out that various new deep-sea research platforms are being developed to augment the existing fleet. Forty years after their first-generation Alvin submarine, the WHOI's next-generation submersible is hoped to be available in 2008 and will be able to reach 6,500 m, similar to the Japanese Shinkai submersible. Tim Shank, a biologist at WHOI, reported that China is also building its first submersible, able to reach 6,500 m, which reflects the country's interest in becoming an international player in deep-sea research.

Another area under development is the use of remote operating vehicles (ROVs) to explore large depths without risking the lives of scientists on board. Shank and colleagues hope to send a hybrid ROV to the Marianas Trench, the deepest part of the ocean with a depth of approximately 11,000 m, in the autumn of 2006. Last year, the NOAA obtained a ship from the US Navy and are now retrofitting it for ocean exploration. It will be able to deploy an ROV that can go as deep as 6,000 m. The July 2005 Lost City expedition to explore the deep-sea vents and 61 m chimneys at the Mid-Atlantic Ridge site, was organized by a consortium of academic, government and commercial partners that includes NOAA, the Graduate School of Oceanography at the University of Rhode Island (Kingston, RI, USA), the University of Washington (Seattle, WA, USA), the University of New Hampshire (Durham, NH, USA), the Mystic Aquarium & Institute for Exploration (Mystic, CT, USA), Electronic Data Systems (EDS; Plano, TX, USA), the US National Geographic Society (Washington, DC, USA) and the JASON Foundation for Education (Ashburn, VA, USA). The expedition allows shore-based scientists nearly 8,000 km away to conduct 'seagoing' research in real-time by using ROVs and satellite transmissions to send live video, audio and scientific data to geologists, chemists, biologists, as well as educators and the public. Shank commented that this could become a cost-saving tool in the future, but it is not yet sufficiently cost-effective. Manley added that the use of more automated instruments will make research cheaper as it allows more work to be done per dive.

The sampling tools on board the submersibles are also evolving. WHOI and NOAA are developing a mass spectrometer that samples water at a depth of 2,000 m and 200 Atmospheres pressure. Similarly, DNA microarrays, coupled with 'lab-on-a-chip' technology, are another potential real-time analytical device that could analyse biological samples directly on board a submarine. However, the physical conditions at such depths pose a considerable engineering challenge. "The plumbing and electronic problems [at that pressure] require very sophisticated valve systems to control the flow of water samples," Manley commented. As with any new technology, these tools will require considerable investments. But, "the cost will come down and the ability to have real-time information is fantastic," Shank said.

that the term 'prospecting', which came into scientific use with the discovery of manganese and other metallic nodules in the 1970s, is misleading. He hates the term being applied to biological living resources and therefore prefers 'biodiscovery'. In addition, the chances of finding something of commercial value are extremely low. "[Someone] will have better luck with the lottery than in pursuing biodiscovery due to the numbers of samples that have to be collected and tested," Newman commented.

**"Most innovations from marine or any biomaterials require considerable research and so the line between marine scientific research and bioprospecting will be fuzzy"**

Mathur also prefers 'biodiscovery' because it better reflects the nature of discoveries that may often not be commercialized and may have only minimal effect on the environment.

According to Johnston, both a meeting of key policy makers in June 2005 and the UNU-IAS report are preparations for a UN General Assembly meeting to draft a resolution about deep-sea research and bioprospecting policy in March 2006. He expects more emphasis on flexibility and benefit sharing in any future deep-sea environmental protection policy the UN General Assembly might adopt, to avoid some of the negative experiences with the UN's CBD agreement. He also suggested that the UN's International Seabed Authority could oversee such policy. Arico pointed out that benefit sharing should

include monetary issues, as well as training and transfer of technology and scientific information, so developing nations could profit from deep-sea research both commercially and scientifically. However, Newman thinks that benefit sharing should be weighted among different partners to cover the relative cost of those who contribute. Johnston added that being able to assess quantitatively where and how much deep-sea research is taking place will also improve the quality of environmental impact assessments.

Not surprisingly, industrial and academic parties have mixed reactions to the value of any future international policy. Mathur was more positive and commented that he was the first industry member to be invited to the UN conference on benefit sharing three years ago. He hopes industry representatives will be invited again to allow them to present their view before any global legislation is passed.

There is still the question whether the UN would be the right organization to oversee regulations of international deep-sea research and biodiscovery. For instance, Shank questioned the effectiveness of any UN policy because “scientists do not think about looking on a UN web page on a daily basis and most probably have not heard of the recent UN document.” Similarly, Stetter conceded that he had not even heard of the UNU-IAS document and commented that any regulation by the UN “smells of bureaucracy”. Newman questions whether a UN policy would have any effect if not all countries translate it into binding national law. He called the UN Convention on the Law of the Sea a “toothless tiger”, which has not stopped overfishing because many nations do not enforce the policy. In addition, Distel pointed out that it will be a very complicated process to get all countries to adopt and adhere to a common policy: “The political and natural [borders] may conflict and complicate the issue of delineating protected areas.”

While the scientists and lawmakers continue to debate whether the UN is the right organization to regulate research, most agree that the scientific community should be looking to the future. As Christoffersen pointed out, there may be much more commercial interest in the deep seas to come. “We don’t have resorts

and hotels in the deep sea yet and it will be decades before that might happen, [but] it is good that efforts for policy have been started because the currently limited deep-sea expedition traffic will probably increase in the next few decades.”

## REFERENCES

- Arico S, Salpin C (2005) *Bioprospecting of Genetic Resources in the Deep Seabed: Scientific, Legal and Policy Aspects*. Tokyo, Japan: United Nations University Institute of Advanced Studies. [www.ias.unu.edu/binaries2/DeepSeabed.pdf](http://www.ias.unu.edu/binaries2/DeepSeabed.pdf)
- BCC (2003) *Biomaterials from Marine Sources*. Study C-184R. Norwalk, CT, USA: Business Communications Company, Inc.
- Haddock SH, Dunn CW, Pugh PR, Schnitzler CE (2005) Bioluminescent and red-fluorescent lures in a deep-sea siphonophore. *Science* **309**: 263
- Huber H, Hohn MJ, Rachel R, Fuchs T, Wimmer VC, Stetter KO (2002) A new phylum of Archaea represented by a nanosized hyperthermophilic symbiont. *Nature* **417**: 63–67

- Lintner K, Lamy F, Mas-Chamberlin C, Mondon P, Scozzi S, Buche P, Girard P (2002) Heat-stable enzymes from deep sea bacteria: a key tool for skin protection against UV-A induced free radicals. *IFSCC Mag* **5**: 195–200
- Stetter KO (1982) Ultrathin mycelia-forming organisms from submarine volcanic areas having an optimum growth temperature of 105 °C. *Nature* **300**: 258–260
- Venter JC *et al* (2004) Environmental genome shotgun sequencing of the Sargasso Sea. *Science* **304**: 66–74
- Vezi A *et al* (2005) Life at depth: *Photobacterium profundum* genome sequence and expression analysis. *Science* **307**: 1459–1461
- Waters E *et al* (2003) The genome of *Nanoarchaeum equitans*: insights into early archaeal evolution and derived parasitism. *Proc Natl Acad Sci USA* **100**: 12984–12988
- Yayanos AA (1995) Microbiology to 10,500 meters in the deep sea. *Annu Rev Microbiol* **49**: 777–805

Laura Ruth

doi:10.1038/sj.embor.7400609

## The engineer’s approach to biology

Engineers’ interest and contributions to molecular biology have sparked a completely new research field: synthetic biology. Despite no commercial applications so far, the prospects for basic research are exciting

In 1998, computer scientist Ehud Shapiro returned to the Weizmann Institute in Rehovot, Israel, as a group leader after a five-year break as a software entrepreneur. At the peak of the Internet boom, it would have been easy to find an exciting topic to pursue in computer science. Instead, Shapiro became interested in the origin of life and began to train himself in molecular biology, which eventually sparked his idea to build computers from biological molecules. His team first constructed a molecular Turing machine based on DNA, restriction nuclease and ligase to perform simple computations (Benenson *et al*, 2001), soon followed by a more sophisticated system that performs stochastic computations using mRNA molecules as input (Benenson *et al*, 2004).

What seems merely to be the intellectual interest of an Israeli computer scientist—

using biological compounds and systems to create logical circuits—has in fact become the hottest area in the biological sciences: synthetic biology. Other engineers are also dropping their soldering guns for micropipettes to rewire genes and genomes with the aim of reprogramming living organisms. “Synthetic biology is the other side of the coin of systems biology,” commented Victor de Lorenzo, Vice Director of the National Centre of Biotechnology in Madrid, Spain. “What you want is to create or recreate systems that have some properties of life from engineering principles.” This includes a range of techniques from recombinant cloning, to synthesizing genomes *de novo*, to creating completely new entities such as Shapiro’s artificial systems. However, more interesting than the technology itself is the ability to create artificial metabolic and regulatory pathways and to