Biotechnology to Improve Health in Developing Countries - A Review

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The growing health disparities between the developing and the developed world call for urgent action from the scientific community. Science and technology have in the past played a vital role in improving public health. Today, with the tremendous potential of genomics and other advances in the life sciences, the contribution of science to improve public health and reduce global health disparities is more pertinent than ever before. Yet the benefits of modern medicine still have not reached millions of people in developing countries. It is crucial to recognize that science and technology can be used very effectively in partnership with public health practices in developing countries and can enhance their efficacy.

The fight to improve global health needs, in addition to effective public health measures, requires rapid and efficient diagnostic tools; new vaccines and drugs, efficient delivery methods and novel approaches to therapeutics; and low-cost restoration of water, soil and other natural resources. In 2002, the University of Toronto published a report on the "Top 10 Biotechnologies for Improving Health in Developing Countries". Here we review these new and emerging biotechnologies and explore how they can be used to support the goals of developing countries in improving health.

Key words: biotechnology - developing countries - global health

In the face of growing global health disparities, the important contribution of science and technology to improving health cannot be overlooked. The fight to improve global health needs, in addition to effective public health measures, requires rapid and efficient diagnostic tools; new vaccines and drugs, efficient delivery methods, and novel approaches to therapeutics; and low-cost restoration of water, soil, and other natural resources. Over the last 100 years, innovations in science and technology have resulted in improved health, quality of life, and a rise in life expectancy worldwide. Yet the benefits of modern medicine have still not reached millions of people in developing countries. It is crucial to recognize that science and technology can be used very effectively in partnership with conventional public health practices in developing countries and can enhance their efficacy.

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Biotechnology has tremendous potential to address health and development issues in developing countries – if we rise to the challenge (Singer & Daar 2001). The University of Toronto's 2002 report on the "Top 10 Biotechnologies for Improving Health in Developing Countries" (Table) discussed the relevance of genomics and related biotechnologies to health (In this review, we will refer to genomics as the powerful new wave of health-related life sciences energized by the human genome project and the knowledge and tools it is spawning). These 10 biotechnologies have been mapped onto the United Nations Millennium Development Goals to provide a compelling illustration of the potential impact of this exciting new field of science on development (Acharya et al. 2003). Here we review these new and emerging biotechnologies and explore how they can be used to support the goals of developing countries in improving health as well as other development indicators. We will review the study methodology that was used to prioritize the "Top 10 Biotechnologies", and describe each technology in turn. Using

TABLE

Top 10 biotechnologies to improve health in developing countries

1. Molecular diagnostics
2. Recombinant vaccines
3. Vaccine and drug delivery
4. Bioremediation
5. Sequencing pathogen genomes
6. Female-controlled protection against sexually transmitted infections
7. Bioinformatics
8. Enriched genetically modified crops
9. Recombinant therapeutic proteins
10. Combinatorial chemistry

relevant examples we will identify ways in which these technologies can be used to achieve specific goals for health and development in developing countries.

METHODOLOGY OF THE TOP 10 BIOTECHNOLOGIES STUDY

The top 10 biotechnologies for improving health in developing countries were identified in a study conducted by the University of Toronto in partnership with an international panel of scientists with expertise in biotechnology and global health issues (Daar et al. 2002). The Panel members were identified through literature searches and with recommendations from individuals at World Health Organization and Rockefeller Foundation. Thirty-nine scientists from both developing and developed countries were invited to take part in the study, 28 of whom completed the project. Approximately half of the panelists were employed in developing countries, and the rest were either originally from developing countries or had experience working in global health. Some of the key developing countries with activity in biotechnology (Brazil, China, Cuba, Egypt, India, South Africa, South Korea) were represented.

A structured process known as the Delphi method was used to bring the Panel to a consensus regarding the identification and ranking of the biotechnologies (Adler & Ziglio 1996). The study spanned three "rounds," which were completed over a period of five months via email, fax, telephone and personal interviews.

In Round 1, the panelists were invited to participate in the project and asked the open-ended question, "what do you think are the major biotechnologies that can help improve health in developing countries within the next 5 to 10 years?" Their answers were analyzed and organized into categories (e.g. diagnostics, drug development, delivery systems), generating a list of 51 technologies. Their descriptions and definitions of the technologies were followed as much as possible, rather than the study team's own preconceptions. As the list was being developed, it was reviewed and modified by three external scientists (not Panel members) to ensure the technologies were mutually exclusive and categorized appropriately.

In Round 2, the list of 51 biotechnologies was reviewed by the Panel for ranking the ten most promising technologies and to provide reasons for their choices, using criteria such as impact of the technology, appropriateness for developing countries, burden of disease addressed, feasibility, creation of new knowledge, and indirect benefits. These rankings were combined (1st = 10 points, 2nd = 9 pts, etc.) to produce a total point score for each technology.

In the final consensus-building round a list of the top 12 technologies, based upon the Round 2 rankings, was sent to the panelists along with a summary of the reasons they had provided. They were given the opportunity to revise their rankings in light of this input. Twenty-eight panelists completed Round 3. The results of Round 3 represent the top 10 biotechnologies for improving health in developing countries in the next five to ten years. The top three technologies showed a high degree of consensus: all but one of the panelists included at least one of these among their personal top three choices. The final ranking of the technologies reflects the consensus of the Panel.

TOP 10 BIOTECHNOLOGIES FOR IMPROVING HEALTH IN DEVELOPING COUNTRIES

Molecular diagnostics

Infectious and parasitic diseases are responsible for nearly 40%, or 17 million deaths every year. The three major killers are HIV/AIDS, malaria and tuberculosis, which together claim at least 5 million lives a year. Rapid and accurate diagnosis of diseases not only increases chances of survival, but also avoids waste of resources on inappropriate treatments and helps prevent further spread of disease. Many conventional diagnostic tools tend to be cumbersome, time-consuming, expensive and sometimes inaccurate. In contrast, modern molecular diagnostics draw upon recent advances in biology to diagnose infectious disease by detecting the presence or absence of pathogen-associated molecules (nucleic acids or protein) in a patient's blood or tissues. The scientific panel in the University of Toronto study ranked molecular diagnostics as the most promising set of technologies for improving health in developing countries over the next five to ten years. Molecular diagnostics are simple, rapid, relatively inexpensive and have high specificity and sensitivity. These include such technologies as the polymerase chain reaction (PCR), monoclonal antibodies and recombinant antigens, discussed below.

PCR-based diagnostic tools are fast, accurate and require minimal volumes of serum or tissue. Amplification and identification of a pathogen-specific DNA sequence in the body fluids or cells of a person identifies infection in that individual. Besides being extremely sensitive, PCR tests can provide results in a few hours, as opposed to days for conventional diagnostics. They can also be used to detect infectious organisms that are difficult or impossible to grow in culture (e.g. *Mycobacterium tuberculosis* or *Plasmodium falciparum*) or are dangerous to handle (e.g. HIV/AIDS) (Louie et al. 2000). A PCR test for three complexes of New World *Leishmania* (*Leishmania braziliensis*, *Leishmania mexicana*, and *Leishmania donovani*) – which cause a spectrum of diseases – was developed in Nicaragua and uses multiplexing techniques to test for more than one disease at once, saving both time and resources (Harris et al. 1998).

Going a step beyond current PCR technology, *nanotechnology* provides the basis of a new method for detecting infectious diseases at the molecular level, without the need for DNA amplification. One nanotechnique uses gold particles complexed with diagnostic DNA oligonucleotides complementary to pathogen-derived sequences. A blood sample is placed between two electrodes in the presence of the probe. The probe anneals to the pathogen sequence if present, and the gold particles close the circuit between the electrodes to produce a detectable signal. This approach is more sensitive than conventional detection methods, and has the potential to be substantially more affordable (Park et al. 2002).

While PCR tests are on their way to finding applications in developing countries, antibody-based applica-

tions are already highly suited to the developing world. In the last few years, the development of simple and rapid antibody-coated dipstick tests have increased the relevance of this technology for the developing world. Dipsticks can be used anywhere, without the need for laboratory facilities, running water or electricity. OptiMAL, an antibody-based dipstick test for malaria, was used during a malaria outbreak in Honduras. It rivaled the accuracy of microscopic analysis, the "gold standard" of malaria diagnosis (Palmer et al. 1998). The Program for Appropriate Technology in Health (PATH), an international not-for-profit organization committed to improving global health, is developing dipsticks for the detection of malaria, tuberculosis (TB), and hepatitis C, among other diseases. It has developed an HIV dipstick test that is now being produced by several private firms in developing countries. Determine® HIV-1/2 is another easy-to-use, rapid test for HIV-1 and HIV-2 antibodies developed by Abbott Laboratories that does not require instrumentation (http://www.pmtctdonations.org/en/products/determine.cfm). The test is accurate and sensitive and has been successfully tested in the field in Ghana.

Recombinant vaccines

Vaccines are arguably the most important medical advance of the last hundred years. Vaccination has resulted in the eradication of smallpox, the imminent eradication of polio, and a dramatic reduction in the prevalence of many other infectious diseases (Widdus 1999). Advances in vaccine research are expected to impact not only communicable diseases, but also non-communicable ones such as cancer.

Recombinant technology makes it possible to have single proteins of a pathogen produced in non-pathogenic microorganisms. This obviates the risks associated with conventional live, attenuated vaccines while conferring immunity against disease. Recombinant vaccines may also prove to be cheaper because of innovative production methods and, potentially, because of improved storage characteristics (such as longevity and resistance to breakdown). Much progress is being made in recombinant vaccine development but there continue to be challenges such as, for example, correct presentation of recombinant antigens to the immune system and lengthening the lifetime of the engineered protein in the body.

A variety of recombinant vaccines exist, the most promising being viral vector vaccines, naked DNA vaccines, and plant-derived vaccines. The subunit vaccine RTS,S/AS02 was recently demonstrated to provide protection against natural malaria infection in adults in a clinical trial in The Gambia (Bojang 2001). For the first nine weeks of the study, 71% of the participants were protected from infection. Clinical trials on children in both The Gambia and Mozambique are now underway (Malaria Vaccine Initiative, 2003). This particular vaccine is synthesized by mice and excreted in their milk. The developers have expressed interest in creating transgenic goats for up-scaling production.

TB is on the rise throughout the world and particularly as an opportunistic infection in developing countries with high HIV infection rates. It claims at least 2 million lives every year. Researchers are actively searching for a potent recombinant TB vaccine (Carol & Sacksteder 2002). Progress to date includes a subunit vaccine based upon the Mtb8.4 surface antigen that protects mice from virulent TB infection (Coler et al. 2001).

Most HIV vaccines currently in clinical trial are recombinant vaccines. There are 28 ongoing trials, involving 24 different vaccines. Of these, 8 are DNA-based, 8 use recombinant viral vectors, 5 are protein subunits and 3 are lipopeptides (International Aids Vaccine Initiative).

Vaccine and drug delivery

Closely related to advances in vaccines are improved methods of vaccine and drug delivery. Currently, most vaccines and many drugs are given by injections. Thousands of children die each year from vaccine-preventable diseases because vaccine delivery requires expensive facilities and trained medical personnel. Cost-cutting through the re-use of needles and other unsanitary practices are known to spread blood-borne infections, particularly HIV and hepatitis. It is estimated that 80,000 to 160,000 new cases of HIV/AIDS, 8 to 16 million new cases of hepatitis B and 2.3 to 4.6 million new cases of hepatitis C are caused each year by the reuse of needles (WHO 2000a).

Injection-free and controlled-release delivery systems could help to solve many of these problems. Needle-free technologies propel the vaccine or drug into the body with a high-speed jet of gas. Solutions, rubbing gels and skin patches use simple diffusion to introduce agents into the body. Another avenue into the body is the mucus membrane that lines all of the inner cavities of the body, including the intestines and the lungs. Drugs and vaccines can be introduced across the respiratory tract through nasal sprays and inhalers.

Refrigerated transport and storage ("the cold chain") is a major expense in all vaccine programs, generally accounting for at least 15% of the budget (Lloyd 2000). A variety of organisms contain the non-reactive disaccharide trehalose that stabilizes them when stressed. For example trehalose stabilizes proteins in *Saccharomyces cerevisiae* cells during heat shock (Singer & Lindquist 1998). It helps brine shrimp (*Artemia* species) survive severe dehydration (Brumfiel 2004). The remarkable properties of trehalose have led to investigation of its use in producing powdered vaccines and drugs that do not need refrigeration. With this and other stable sugars, researchers have been able to dehydrate liquid vaccines and drugs and store them at room temperature for up to several months without affecting their potency. Associated injection devices for dried vaccines have been developed. Some involve the reconstitution of the dried substance into a liquid just prior to injection, while others introduce the substance into the body as a powder using needles or a high-speed jet of gas.

Drug delivery could also be improved by new technologies that reduce the number of doses required for treatment. Long and complicated drug regimens are difficult to comply with, especially if they involve visits to medical facilities. When patients fail to complete their treatments, they not only fail to recover, but partial treatment

can lead to the emergence of drug resistant strains of disease. Controlled-release drugs and vaccines can be introduced into the body in association with a biodegradable polymer that releases its contents gradually as it is broken down by the body. Researchers recently reported the successful development of room temperature stable, controlled release formulations of oligosaccharide ester derivatives (OEDs) of trehalose and a synthetic peptide analogue of hepatitis B surface antigen (Moynihan et al. 2002). One example involves *M. tuberculosis*, which is rapidly acquiring drug resistance because many patients do not complete the several month-long antibiotic treatment regime. Multi-drug resistant tuberculosis is also becoming a problem in several developed countries. Sustained-release antibiotic treatments, which automatically release their contents overtime, would lower the number of doses a patient must receive, thereby increasing compliance and limiting the emergence of drug resistant strains of TB. Preliminary studies of controlled release antibiotics have been promising (Korkusuz et al. 2001).

Bioremediation

Bioremediation leverages the natural biochemical processes of plants or micro-organisms to clean up the environment. Bioremediation has direct significance to any development activity related to the environment, including water, soil and air. For instance, the use of bioremediation to clean contaminated soil or water can promote food production, and can prevent the spread of infectious water-borne diseases.

Two main types of pollution threaten the health and well-being of human populations: organic waste and heavy metals such as lead, mercury and cadmium. Bacteria can detoxify both. Plants can break down most forms of organic waste, and can store harmful metals in their tissues, therefore making it easier to collect, harvest and even recycle metal waste. Water contaminated by human waste harbors large populations of pathogenic organisms and has been implicated in the transmission of cholera, typhoid, hepatitis A, and other waterborne diseases. The incidence of these diseases can be dramatically reduced through sewage treatment. Conventional chemical sewage treatment can be augmented by the use of beneficial bacteria and other microorganisms to kill pathogens. A number of low-cost alternatives to conventional sewage treatment have been developed, such as one that is now in use in Southern China. This system uses floating rafts called Restorers to supply beneficial microorganisms to a canal contaminated with human waste (Oceanarks International), transforming the sewage canal into a wetland featuring over 20 species of native Chinese plants.

Bioremediation technologies can also be used to reduce environmental pollution associated with heavy industries, including oil spills, acid mine drainage, and radioactive waste. In Brazil, the Federal University of Santa Catarina and Petrobras, the Brazilian national oil company, have jointly taken steps to address the degradation of benzene, toluene, ethylbenzene, and xylene (BTEX) from oil spills (Lehmann 1998). Phytoremediation of BTEX is now under development, which uses the willow tree (*Salix babylonica*) cultivated hydroponically for bioremediation of gasoline spillage (Corseuil & Moreno 2001). Laboratory studies indicate that the plants were able to reduce ethanol and benzene concentrations in water by more than 99% in less than a week.

Bangladesh is currently facing "the largest mass poisoning of a population in history" due to naturally-occurring groundwater arsenic contamination (WHO 2000b). At least 100,000 cases of debilitating skin lesions are believed to have already occurred because of the seepage of arsenic into the water supply, and at least 50 million people are at risk. Recently discovered in a gold mine in Australia, a bacterium named NT-26 may be able to help (Santini et al. 2000). NT-26 has the natural ability to transform arsenite or As(III), which is relatively soluble and extremely toxic, into the much less toxic form arsenate. The Australian Research Council is supporting research to investigate the potential of NT-26 to reduce the toxicity of arsenic dissolved in water, and Genome Canada is spearheading the whole-genome sequencing of this organism.

Researchers at the University of Florida have discovered that the brake fern *Pteris vittata*, has a remarkable ability to accumulate arsenic in extremely high concentrations without any apparent harm to itself (Ma et al. 2001). The unusually sun-loving fern could be cultivated in arsenic-contaminated water and act as a natural arsenic filter. The fern collects the arsenic in its fronds, which are easy to harvest, although scientists admit that more work is needed on how to dispose of the plants. Further research is also looking into identifying and then splicing the fern's arsenic-metabolizing genes into other plants.

Sequencing pathogen genomes

Pathogen genome sequences, together with bioinformatics (discussed in detail below), can rapidly accelerate the process of drug discovery and are important tools in the fight against infectious diseases. For example, in a comparison of disease-causing and benign strains of the same organism, genes unique to the virulent strain are likely to play an important role in pathogenesis, and the proteins for which they code may be useful drug targets (Loferer 2000).

Innovative researchers have taken advantage of genomics to take the little-used antibiotic fosmidomycin off the shelf and bring it into clinical trials for malaria. Scanning the *P. falciparum* genome revealed a potential target gene that bears homology to the target gene of fosmidomycin. This has given rise to a new class of antimalarial drugs that is currently in clinical trials (Jomaa et al. 1999). The sequencing of the genome of *Anopheles gambiae*, one of the species that transmits malaria, may also provide avenues for controlling malaria (Balter 2001).

In addition to spurring novel drug discovery, pathogen genomics has also given a boost to the development of vaccines. Numerous vaccine candidates for serogroup B meningococcus were discovered by searching the organism's genome. Of the 570 antigens found, 85 showed promise when used to immunize mice (Pizza et al. 2000).

Another application of pathogen genomics involves a serious health concern worldwide – the emergence of pathogen resistance to previously effective drugs. Analysis of pathogen genomes could reveal the genes play a

role in helping these organisms develop drug resistance and point researchers in the direction of treatments that can overcome the action of these genes. For example, by comparing the genomes of resistant and nonresistant strains, or by analyzing the genes at work in the drug resistant stage of an organism's lifecycle, scientists can identify key genes that play a part in drug resistance (Cowman 2001).

Female-controlled protection against sexually transmitted infections (STIs)

A decade ago, the World Bank ranked STIs as the second major cause of ill health among women aged 15 to 44, accounting for 8.9% of their disease burden, compared to 1.5% in men (World Bank 1993). For a variety of reasons – socio-economic, cultural, and biological – women are more vulnerable to infection than men (WHO 2000c). Women with STIs often bear heavy social stigma, and they usually do not have resources (time or money) to seek health care. It is an accepted fact that improving the health of women has a positive impact on their children, on their community, and indirectly on a country's development.

Despite the seriousness of this problem, women currently have few means of protection. The male condom requires male consent, which many women are unable to negotiate in their relationships. The female condom is costly and indiscreet. More promising options include externally applied vaginal microbicidal creams or gels, which block the transmission of infection across the vaginal wall. Carraguard is one such vaginal microbicide that is in development. It is currently in phase III trials, one of the first products of its kind to enter this advanced phase of research (Population Council). The National Institute of Allergy and Infectious Diseases (NIAID) of the United States has focused on two microbicides: BufferGel, which acts by maintaining the normal acidity of the vagina, and PRO2000, which inhibits viral entry into cells. Phase I trials of both products have shown them to be relatively safe and well-tolerated (Van de Wijgert 2001).

Most recently, the Bill & Melinda Gates Foundation have made a $US 60 million grant to the International Partnership for Microbicides (IPM) to accelerate the discovery, development, and accessibility of topical microbicides to prevent HIV transmission. This grant is the largest ever made to support microbicide research. IPM also received a grant of $US 15 million from the Rockefeller Foundation. The company is expected to deliver a safe and effective product by the end of this decade.

Externally applied antibodies have also shown significant promise in blocking STI transmission. Monoclonal antibodies have been shown to provide protection against HIV, Herpes Simplex Virus 1 and 2, Hepatitis A and B and chlamydia (Zeitlin et al. 1999).

Another alternative to synthetic microbicides could be a genetically-modified strain of *Lactobacillus*, which normally inhabits the vagina (Blakesless 1998). Recombinant *Lactobacillus* could synthesize the compound CV-N, which has been shown to bind to and inhibit all known strains of HIV. It was discovered by researchers at the National Cancer Institute of the United States in the blue-green algae *Nostoc ellipsosporum* (Boyd 1997). CV-N has been found to not irritate the vagina, and researchers are hopeful that this genetically modified organism may function as a safe and affordable vaginal microbicide.

Perhaps the ideal method of female-controlled protection against STIs is vaccination. Vaccines afford extended, often life-long protection and also have no impact on the sexual encounter and do not entail a contraceptive effect, unlike, for example, the condom. As of October 2003, there were seven HIV/AIDS vaccines currently in clinical trials, and all seven are products of biotechnology (Pipeline Project UCSF). The majority among the seven are viral vector vaccines and naked DNA vaccines. Heptatitis B, the only STI for which a vaccine exists, is a recombinant vaccine synthesized in *Saccharomyces cerevisiae*. Recombinant vaccines are currently being developed against numerous STIs, including human papillomavirus (HPV), chlamydia, gonorrhea, and hepatitis C (Fletcher 2001)

Bioinformatics

Bioinformatics is the application of computer hardware and software to store, retrieve and analyze large quantities of biological data. High throughput technologies (DNA sequencing machines, DNA and RNA microarrays, combinatorial chemistry, 2D gel electrophoresis, and mass spectrometry) yield vast quantities of biological data. Bioinformatics organizes this sea of biological data into meaningful databases and conducts sophisticated computer analyses ("data-mining") to generate answers to research questions.

Biological databases are central to bioinformatics. Major bioinformatics databases have been established as public resources available to all via the Internet. GenBank is a massive online database of all publicly available gene sequencing that can be accessed free of charge over the Internet. GenBank exchanges data with the DNA DataBank of Japan (DDBJ) and the European Molecular Biology Laboratory (EMBL) on a daily basis. Several other databases exist, examples of which include the protein sequence database SWISS-PROT, the Molecular Modeling Database (MMDB) and the *Anopheles* database AnoDB.

Bioinformatics applies computer algorithms to transform large-scale biological data into useful information. Without bioinformatics, the task of mining genomics data would be extremely laborious and error-prone, and it would take several years to realize the potential of genomics. Like data, many algorithms are shared worldwide and available free over the Internet along with basic tutorials. They can generally be found on the websites of public bioinformatics databases.

One of the key applications of bioinformatics to diseases is the accelerated discovery of drug targets. Comparative genomics can also be used to identify drug targets and also serve to identify those genes that vary least between different strains of a virus (Loferer 2000). These stable (non-mutating) genes may make effective, long-lasting drug targets because they are likely to be necessary for the organism's survival and have not demonstrated a tendency to mutate (Lyall 1996).

Besides identification of drug targets, bioinformatics

can also play an important role in drug design. Information on the three dimensional structure of the target molecule is required for the rational design of a drug that interacts with the target appropriately and effectively. The 3-D structure of a novel target can be elucidated by comparing putative targets with proteins of known structure. Bioinformatics can also boost discovery of vaccine candidates. For instance, in their analysis of *Chlamydia pneumoniae*, which is intrinsically challenging to study using conventional laboratory techniques, researchers identified 147 cell surface proteins (Grandi 2001, 2003). Of these, 58 induced an immune response in mice.

Bioinformatics is a useful entry point for developing countries in the field of biotechnology. It is a relatively small investment, compared with the costly laboratory facilities and instrumentation required for life sciences research. It does require investment in training of human resources and building research capacity to study genomic sequences and biochemical pathways using bioinformatics. One compelling reason to take advantage of this opportunity is that the majority of R&D in developed countries is not directed towards infectious diseases that affect developing countries. Such initiatives are already being taken in several developing countries.

To meet the worldwide demand for skilled bioinformaticians, a free accredited course in bioinformatics is now being offered over the Web by a consortium of six universities called S-Star.org. Another example is the Special Program for Research and Training in Tropical Diseases (TDR), an independent global program of scientific collaboration, established in 1975 and co-sponsored by the United Nations Development Program, the World Bank and the World Health Organization. In 1994, The TDR launched an initiative to develop capacity in bioinformatics in developing countries in 2001. The rationale was that capacity in bioinformatics is required for both basic research as well as the development of new biotechnology applications in disease control. As a first step – "training the trainers" – the International Training Course on Bioinformatics and Computational Biology Applied to Genome Studies was the held in 2001, in Brazil. The objective was to develop a multi-disciplinary and international network for bioinformatics applied to pathogen genome research and to prepare participants to teach similar courses in their home countries. The next steps are to initiate regional training courses in Africa, Asia, and Latin America, and a Bioinformatics Career Development Grant for exceptional scientists identified from these courses. In the longer term, Masters and Doctoral training programs will be developed. Four centres in South Africa, Brazil, India, and Thailand have been selected to provide regional training courses in bioinformatics. Despite the fact that TDR's bioinformatics initiative is quite young, considerable progress has already been made in strengthening institutions and training researchers from developing countries, helping them to reach self-reliance in this field of modern biological research (Oduola et al. 2002).

A similar effort has been initiated at the South African National Bioinformatics Institute (SANBI) at the University of the Western Cape, South Africa: the Bioinformatics Capacity Development Research Unit. This initiative recognizes the competitive opportunities in bioinformatics for smaller, less developed countries since bioinformatics does not require prohibitive infrastructural investment. SANBI provides a focus for biological research located in Africa and focused on Africa and African concerns. Its goals include the development of an online specialized resource for genomics and genome informatics; capacity development in genomics and bioinformatics in South Africa; and the development and implementation of genome annotation methods. The Unit aims to heighten awareness of bioinformatics in South Africa and to assist the country in making optimal use of this technology. It offers services in databases – nucleotide, protein, structure (including the human genome sequence and derived data); software tools for bioinformatics/genomics; countrywide training in bioinformatics and genomics; and a bioinformatics support network of South African scientists. The first workshop for African scientists on Bioinformatics, held last year, attracted scientists from several African countries. A bioinformatics network of researchers in seven African countries has been established with the Unit as the hub.

Enriched genetically modified crops

Over half of all infant deaths in developing nations are associated with a lack of essential vitamins and nutrients (WHO, Nutrition). Malnutrition also causes impaired cognitive and physical development, and is associated with multiple illnesses attributed to specific nutrient deficiencies, such as anemia, caused by iron deficiency – one of the leading causes of maternal mortality (UNFPA 2001). Furthermore, malnutrition adversely affects the immune system and amplifies the effects of infectious diseases.

Genetic modification makes it possible to introduce new genes and new traits into crops more rapidly and more precisely than traditional breeding and also enables the introduction of new genes from different species. Various traits can be introduced into crops through genetic modification. This has tremendous potential advantages, especially in the creation of nutritionally-enhanced crops. More than 300,000 children go blind every year from vitamin A deficiency, and two-thirds of these children die. Many are children of small farmers or farm workers too poor to afford a highly diversified diet. One effective way of combating their vitamin A deficiency is to increase the vitamin A content of their staple food. This was the primary impetus for the development of rice modified to express elevated levels of β-carotene and iron, known as "Golden Rice". Golden Rice stands apart as a model example of the use of gene technology to enhance the nutritional value of a staple food crop (Ye et al. 2000).

More recently, researchers in India have developed a potato rich in all essential amino acids (Chakraborty et al. 2000). This potato contains the albumin gene AmA1 (derived from the South American plant amaranth) that codes for albumin, which contains high levels of all essential amino acids. It gives ordinary potatoes a third more protein than normal, including substantial amounts of lysine and methionine. A lack of these essential amino acids can have an adverse effect on development in children. For example, too little lysine can affect brain development.

This enriched potato is also particularly relevant for India, where a large percentage of the population is vegetarian (Coghlan 2003). The potato is in the final stages of testing, and it has been submitted for official approval. Researchers have also modified lettuce by inserting rat cDNA encoding L-gulono-γ-lactone oxidase, which converts a precursor molecule into Vitamin C (Jain & Nessler 2000). They observed up to a seven-fold increase in the amount of vitamin C in the plant's tissues.

Recombinant therapeutic proteins

As poorer nations move through a process of development and associated demographic change, they face a double burden of disease: to the ever-present problem of infectious diseases is added the burden of non-communicable diseases more commonly associated with the developed world. Non-communicable diseases now account for 60% of all deaths in developing countries, and current trends suggest this number will reach 73% by 2020 (WHO, Noncommunicable Disease Prevention). Therapeutic proteins are used to treat many non-communicable diseases, and the technology to make recombinant therapeutic proteins was ranked ninth among the most promising biotechnologies for improving health in developing countries within the next five to ten years. Affordable and sustainable sources of therapeutic proteins for treating chronic disease are therefore critical.

Recombinant technology makes it possible to insert a gene or genes for therapeutic protein into a suitable organism. Yeasts reproduce quickly and easily and have an advantage over bacteria in their ability to carry out many forms of post-translational protein modification. Because of its safety and familiarity, *S. cerevisiae* is the most popular yeast as recombinant protein factory. The use of plants for this purpose is on the increase – they can be grown in large quantities at low cost, and their use also minimizes ethical concerns and risks associated with animal viruses and bacterial toxins. To date, however, transgenic plant expression systems have relatively low protein yields. Another disadvantage is the difference between plant and mammalian post-translational modifications. Unlike human proteins, plant proteins are not usually glycosylated. Scientists are working to overcome this barrier by creating transgenic plants capable of glycosylation (Bakker et al 2001).

Transgenic mammals are currently the most attractive source of recombinant therapeutic proteins. These animals secrete recombinant protein in an easily-harvested body fluid, such as milk or urine. To limit the secretion of the protein to a particular tissue, the gene is linked to a promoter sequence that promotes the expression of the gene only under conditions typical of the relevant target tissue. It has been estimated that the use of transgenic animals to synthesize recombinant therapeutic proteins would be four to five times cheaper than using mammalian cell cultures (Breekveldt & Jongerden 1998).

Some recombinant therapeutic proteins that would be relatively significant for developing country diseases include erythropoietin for the treatment of anemia, alpha interferon for the treatment of viral infections and leukemia, and insulin for the treatment of type I diabetes. Recombinant human insulin is currently produced in roughly equal proportions by bacteria and yeast. Previously, all insulin was harvested from the pancreas of pigs and cattle, which induced allergic reactions in some diabetics. The two main advantages of recombinant insulin over animal-derived insulin are its chemical, biological and physical similarity to human insulin, and the low risk of transmitting animal pathogenic infections. The patent on recombinant human insulin expires in January 2003, opening the door for entrepreneurs in developing countries to manufacture the product locally and supply the public with the recombinant protein at a more accessible price. In August of 2003, Wockhardt Limited launched India's first recombinant human insulin product, making Wockhardt just the fourth company in the world – and the first outside the US and Europe – to develop, manufacture and market recombinant insulin. This move has also made India the first Asian country to develop this complex technology. Until now, 90% of insulin in India has come from pigs or cows. India has the world's largest population of diabetics, with an estimated 30 million people suffering from the disease, and the Indian market for insulin is valued at around US$ 52 million. Wosulin, Wockhardt's brand of recombinant human insulin, is priced at US $ 2.70 per unit, cheaper than recombinant insulin offered by multinational drug companies in India at US $ 3-5.50 per unit (Express Pharmapulse 2003).

Combinatorial chemistry

Combinatorial chemistry has revolutionized the pharmaceutical industry over the past two decades. There are many diseases prevalent in the developing world for which effective and affordable treatments are lacking, most notably HIV/AIDS. Other diseases, such as malaria and tuberculosis, are acquiring resistance to the only treatments available. Combinatorial techniques can be used to provide new or strengthened medications for these diseases by accelerating drug discovery. They also promote entrepreneurship by helping industries in developing countries become competitive and economically viable in the global market. The increase in efficiency also potentially decreases costs, wastes less material and creates fewer by-products – all of which serve to protect the environment.

Two new classes of drugs against leishmaniasis were discovered using a combinatorial process that produced over 150,000 different compounds (Graven et al. 2001). Leishmaniasis is a potentially fatal disease that is estimated to affect 12 million people around the globe. Researchers also used combinatorial chemistry to focus in on a more potent version of vancomycin, an antibody of last resort against which many diseases are acquiring resistance (Nicolaou et al. 2001). The most successful compounds in the library outperformed the most powerful antibiotics on the market. A third example involves a drug for the treatment of heart disease, which is on the rise in developing countries. Researchers produced approximately 250 versions of a promising drug, one of which was RWJ-53308, which completed Phase II clinical trials in 2000 (Hoekstra et al. 1999).

The International Centre for Science and High Tech-

nology at the United Nations Industrial Development Organization is dedicated to the capacity-building and transfer of technology to developing countries, in recognition of the fact that competitive industrial capability relies on scientific expertise (Miertus & Fassina 1999). Within the field of Pure and Applied Chemistry, ICS focuses, among other areas, combinatorial chemistry methods, and technologies. ICS emphasizes the importance of combinatorial chemistry for the rapid and efficient development of new chemicals – pharmaceuticals, agro-chemicals, and new materials. The tools used by ICS to achieve transfer of know-how include organization of training events, distribution of information packages, networking and offering of fellowships for researchers to learn hands-on techniques, and other methods.

Médecins Sans Frontières (MSF) has committed US $25 million over 5 years for a new initiative to develop drugs for diseases of the developing world that have largely been neglected by research institutions in the developed world. Examples are sleeping sickness, leishmaniasis, and Chagas disease. MSF plans to run the Drugs for Neglected Diseases Initiative (DNDi) like a virtual pharmaceutical company. It will use the experience and resources, both financial and human, of institutions and facilities worldwide, by creating a global network of researchers. DNDi will draw upon the research capacity of the Oswaldo Cruz Foundation (Fiocruz) of Brazil, the Indian Council of Medical Research (ICMR), the Kenya Medical Research Institute (KEMRI), and other established research institutions from the developing world. DNDi will also rely on the public health systems in these countries for access to patients and to organize high-quality clinical trials. The collaborative platforms created by this initiative allow contributions from various groups in each country towards the development process. For instance, research groups might share lead compounds across nations. One example is the development of artemisinin combination therapy for chloroquine-resistant malaria, a collaborative effort between Malaysia, Brazil, Africa, and France. The project, established in 2002, is funded by the European Union and managed jointly by the Special Programme for Research and Training in Tropical Diseases (TDR) and DNDi. As a result of this collaboration, this year there are two combinations ready for toxicology testing.

SUMMARY

This review shows how ten prominent biotechnologies can contribute to improving health in developing countries within the next ten years and can make diverse and significant contributions to the efforts of these countries in improving health and development indicators. Through the provision of simpler and robust diagnostics, new vaccines, safer methods of vaccine and drug delivery, empowerment of women, methods of environmental remediation and other techniques, the benefits of modern technology can reach the developing world. The examples described here indicate how genomics can promote development and reduce poverty, both by improving health and by forming the basis of new industries in developing countries.

Identification of health needs and the role such new technologies can play in addressing them is the first step in the process of harnessing biotechnology for improving health in developing countries. The next step is the implementation of these technologies in the developing world. A number of factors may be responsible for the relative failure of new technologies becoming widely implemented in the South, among them lack of resources, poor scientific capacity and ineffective policies. The challenge now facing us in our quest for greater global health equity is to understand the barriers to implementation of new advances in science and technology in developing countries and to develop mechanisms to break these barriers down. A number of efforts are currently ongoing that can help further our understanding of these mechanisms. The Inter-Academy Council (IAC), created in 2000 to bring together international science academies to discuss the scientific aspects of problems of global concerns, recently put forth a report early in 2004. This report underscores the urgent need to mobilize scientific knowledge to address critical world issues such as poverty, disease, trade and economic transformation. The Millennium Project's Science and Technology Task Force will be presenting its interim report to UN Secretary General Kofi Annan in summer this year. The report identifies four priority areas that require policy decisions: managing technological innovation in a rapidly globalizing world; redefining infrastructure development as a foundation for technological innovation; building human resources in the scientific, technological and engineering sciences through institutions of higher learning; and enhancing private enterprise though the creation and expansion of businesses (including the effective use of intellectual, human, financial and social capital). The contribution of the private sector is highlighted in the report of the UN Commission on Private Sector and Development. The report, titled "Unleashing Entrepreneurship: Making Business Work for the Poor", observes that the process of commercialization for development involves the dissemination and facilitation of knowledge flows between public and private sectors of both developed and developing markets. The report recommends action in both the public and privates spheres, but also emphasizes the linkages between these spheres, recognizing the importance of cooperation and partnerships to achieve goals. Recently, Canadian researchers have proposed an initiative – Canada Science International – to launch Canada as a world leader in developing and applying technological innovations to help solve health and environmental problems in low and middle-income countries in partnership with them. The Canadian government, led by Paul Martin, aims to spend 5% of R&D investments on a knowledge-based approach to development. This provides a rare opportunity both for Canada to leverage its existing investments in S&T innovation to help address the challenges of the developing world, as well as for developing country partners to engage in this innovation process.

All these initiatives point towards strategies for building knowledge economies that foster scientific innovation. The over-arching question raised by both these reports is how a country can build its national system of

innovation. A country's national system of innovation (NSI) represents the institutions that contribute to the creation, diffusion, and use of new economically useful knowledge and the linkages and synergies between the institutions (Lundvall 1992). These institutions not only include formal ones like firms, universities, research centers and government, but also institutions in a wider sense, such as social norms and laws. The Canadian Program in Genomics and Global Health is in the process of conducting a novel study of the health biotechnology innovation systems of Brazil, China, Cuba, Egypt, India, South Africa, and South Korea, all of which have relatively active biotechnology industries. It will focus on identifying the main actors in the health biotechnology innovation systems under study, i.e. by examining the roles of government, private firms, R&D system, the education system etc in the health biotechnology innovation process. The study will also explore the extent and patterns of linkages between all the actors in the NSI systems. Where linkages extend beyond national boundaries, information will be collected on the role of international linkages in the development of genomics/health biotechnologies in these countries. The results of this study may yield useful information for developing countries looking to harness the benefits of biotechnology for development.

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