Small but tenacious: South Africa's health biotech sector

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Despite a challenging business environment, entrepreneurial health biotech companies in South Africa are finding ways to succeed.

Shaped by a complex past, including decades of apartheid rule that divided its population and polarized resources along racial lines, today's South Africa has characteristics of both a developed and a developing nation. It is the strongest economy in the region, accounting for over 30% of Africa's gross domestic product[1] while being home to only a small fraction of its population (48 million people out of nearly 950 million); at ~$11,110, its gross domestic product per person (based on purchasing power parity) is much higher than the African average[2]. It has world-class universities and research institutions—for example, the University of Cape Town was recently ranked 179 in the world (ref. 3)—high-quality hospitals, robust transport infrastructure, strong regulatory and financial systems as well as a tradition of technological strength (in mining and defense, in particular).

In parallel, however, South Africa faces a considerable set of social problems: one of the most unequal distributions of income in the world[2], mass unemployment, a shortage of skilled labor and endemic poverty. In the health field, South Africa's burden of disease is substantial and, for some indications, worse than other countries in sub-Saharan Africa. It has the most people living with HIV of any country in the world (5.54 million people according to estimates from 2005; ref. 4) and the seventh-highest incidence of tuberculosis, with an alarming recent increase in cases of extensively drug-resistant tuberculosis[5]. Other leading causes of death are cerebrovascular disease, ischemic heart diseases and lower respiratory infections[6].

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These circumstances have created a unique environment for the growth of a South African health biotech industry. Well positioned to address diseases of the developing world, South Africa also has the potential to develop niche health products for global markets, drawing on its R&D base, expertise in first-generation biotech (the use of wild-type or natural organisms to produce a product) and great biodiversity. These and other factors lie behind the relatively recent drive to build a local biotech industry to address not only human health, but also food security and environmental sustainability and to act as an engine of job and wealth creation. The key policy driver was the 2001 Department of Science and Technology's National Biotechnology Strategy[7], which allocated 450 million rands (R), or $58 million, in public spending for the years 2004–2007. An important outcome of the National Biotechnology Strategy was the creation of Biotechnology Regional Innovation Centres, or BRICS, which were mandated to identify and develop commercial opportunities in biotech. These are Cape Biotech (Western Cape), Lifelab (KwaZulu Natal) and BioPad (Gauteng), and a national innovation center for plant biotech, PlantBio (Pietermaritzburg). The BRICs, along with two life sciences incubators—eGoli Bio (Johannesburg) and Acorn Technologies (Cape Town), which were established through an earlier government initiative called the Godisa Trust (now SEDA, the Small Enterprise Development Agency)—represent the main dedicated public sector instruments to stimulate and grow private sector biotech activity, particularly through realizing the commercial potential of South Africa's considerable R&D assets. Acorn Technologies was recently amalgamated into Cape Biotech and no longer exists as an independent organization.

Commitment to developing a South African bioeconomy, "from farmer to pharma," has been reasserted more recently by the government's ten-year plan for innovation (2008–2018)[8], which set a new R&D spending target of 2% of gross domestic product by 2018 (gross expenditure on R&D is now 0.92% and expected to reach a goal of 1% by the end of 2009). On the

The offices of Kapa Biosystems in Cape Town; nearby is Cape Biotech, the Biotech Regional Innovation Centre (BRIC) for the Western Cape.

The authors with Patrick Tippoo, R&D Manager at the Biovac Institute in Cape Town. Biovac supplies all of South Africa's vaccine needs and exports small volumes to other countries in the region. Left to right: Sara Al-Bader, Patrick Tippoo and Sarah Frew.

macroeconomic side, since 1994, South Africa has taken several steps to stimulate industrial development. It has opened up to the global economy, liberalized domestic markets and worked toward ongoing macroeconomic stability. The country has a solid culture of patent protection in line with international norms; as a member of the World Trade Organization (Geneva), South Africa's intellectual property regulation was brought in line with TRIPS (Trade Related Aspects of Intellectual Property Rights) in 1997.

An earlier study by our group[9] examined the health biotech innovation systems of seven developing countries, including South Africa. In that study, key challenges identified to the development of a South African biotech innovation system were lack of human resources, low amounts of venture capital and inadequacy of intellectual property (IP) protection for indigenous knowledge. Building on this research, we focus here on activity in the private sector, a key driver of innovative activity.

We present the results of case-study research carried out in 2006–2007 on 16 health biotech companies in South Africa, almost all in the small and medium-sized enterprise (SME) category, and with a focus on companies that innovate in the technologies they develop or the business strategies they use. It is the fourth in a series of explorations of the domestic biotech private sectors in several innovating developing countries; earlier papers have looked at India[10], China[11] and Brazil[12].

We identified companies through consulting literature resources, industry reports and experts familiar with the South African biotech industry. Compared with other countries previously studied by our group[10–12], South Africa's health biotech industry is still small and activities are very diverse. Recent surveys of the biotech landscape demonstrate this[13,14]. For example, the most comprehensive biotech survey so far, carried out in 2003 by the eGoli Bio incubator and the Department of Science and Technology, puts the number of companies with biotech as their core business at 47, of which 39% were in the human health field[13]. Our sample therefore covers most private sector biotech activity in human health therapeutics, prophylactics and diagnostics. Unlike our previous studies[10–12], we also included in our sample several companies working in other areas. Device companies were considered because they represent a comparatively large proportion of the South African biotech sector for both historical reasons—the first human heart transplant was performed at the Groote Schuur Hospital in Cape Town in 1967, and since then, the country has developed clinical and scientific expertise in cardiovascular stents—and because the short business timelines for device startups can be more attractive to investors. To complete the picture of the diverse South African health biotech landscape, we have also included some companies working in the nutraceutical area, which can also offer faster commercialization prospects. More details on our methods can be found in **Supplementary Methods** online.

The aim of the research presented here is to provide an overview of private sector health biotech in South Africa. After providing a detailed analysis of companies in the sector, we discuss the opportunities and challenges that lie ahead for biomedical ventures.

Products and services

Our study revealed that companies in the South African health biotech sector offer a range of products and services (**Table 1**). Below, we present an overview of health biotech companies in the country sorted into five categories: vaccines and biogenerics; therapeutics; nutraceuticals; reagents, diagnostics and medical devices; and contract services.

Vaccines and biogenerics. The Biovac Institute (Cape Town; see **Box 1**), a public–private partnership between the South African Department of Health and the Biovac Consortium (Cape Town), is the only manufacturer of vaccines in sub-Saharan Africa. Biovac's mandate is to supply all of South Africa's Expanded Program of Immunization vaccines, including DTP (diphtheria, tetanus and pertussis), measles, polio, oral polio, bacille Calmette-Guérin (BCG) and recombinant hepatitis B virus surface antigen (HBsAg) vaccine, either by importing directly from overseas or by formulating and filling locally under good manufacturing practice (GMP) conditions. As of early 2008, Biovac's production of the HBsAg vaccine using bulk recombinant antigens from Cuba represented the first vaccine to be manufactured in sub-Saharan Africa since 2001 and marked a milestone in African vaccine self-sufficiency and capacity-building. Biovac's vaccine pipeline includes a pentavalent combination vaccine (DPT + HBsAg + *Haemophilus influenzae* type b (Hib) vaccine) in one vial, which will be easier to administer than the current regime (which requires two injections and the reconstitution of Hib before use). Biovac also supplies surrounding countries, such as Swaziland, Namibia and Botswana, and in due course, it aims to apply for World Health Organization (WHO; Geneva) prequalification so it can access other markets.

Although the provision of competitively priced vaccines for domestic and regional markets is clearly a principal objective for Biovac, it is not the company's only goal. Biovac also is working to build a local skills base in vaccine production and is investing in key infrastructure for the future. According to Patrick Tippoo, R&D Manager of Biovac, "We have to be competitive, but our primary driver is to build local capacity. The definition of value can't be a narrow one; it can't only be measured in rands and cents." Thus, local production of HBsAg vaccine remains a long-term goal, even though it is unlikely to result in cost savings compared with continuing to import HBsAg product.

As in the other countries featured previously[10–12], generics manufacturers in South Africa are helping to fight infectious diseases through supplying more affordable drugs, and >70% of sub-Saharan Africa's estimated $1 billion in annual pharmaceutical production is concentrated in South Africa. In the field of biogenerics, the key South African player is Bioclones (Cape Town; **Box 2**), which markets Repotin (epoetin-α), the first recombinant human erythropoietin (EPO) in the world to be made in baby hamster kidney cells. EPO is indicated primarily for the treatment of anemia due to renal failure, chemotherapy or antiretroviral treatment, and Bioclones has had part of the South African state tender (government contract) for the drug for the past nine years,

Table 1 South African companies interviewed and their product and technology portfolios

Innovative SMEs

Company or organization	Products on the market	Products under development	National or international quality certification
Altis Biologics	Endogen IT (low-molecular-weight fraction of allogeneic human bone extract enriched for mixture of BMPs) for use as implant in complex fractures and bone disease. Manufactured at Tshwane University of Technology Centre for Tissue Engineering and sold through Bone SA.	OBM (low-molecular-weight fraction of porcine bone enriched for BMPs) for use as implant in bone graft procedures. Altis is pursuing South African market as well as obtaining CE mark	GMP-certified by MCC, a member of PIC/S manufacturing facility for manufacture of porcine BMPs for human use; pharmaceutical manufacturing license
AngioDesign	None	Applying structure-guided design to synthesize new domain-selective angiotensin-converting enzyme inhibitors for cardiovascular and other diseases	None
Arvir Technologies	None	Biocatalytic plus chemical process for cost-efficient production of thymidine, a precursor to antiretroviral drugs. Developing 3 undisclosed phytopharmaceutical leads from CSIR's bioprospecting program with *in vitro* efficacy against HIV.	None
Bioclones	Repotin 2000, Repotin 4000 (2,000 or 4,000 IU per ml recombinant human EPO derived from baby hamster kidney cells; epoetin-α)	Retro-inverso peptide analogs of antigens, protease resistant and thermostable, for use in vaccine development. Building capacity to isolate, grow, antigen pulse and mature human dendritic cells to create autologous dendritic cell vaccines.	Cell culture facility GMP-certified by MCC
Biomox	Bio Boost (dietary supplement containing L-methionine, magnesium, vitamin B6, vitamin B12 and folic acid) and 11 other dietary supplements. Contract GMP manufacture of natural products	Extensive formulation work on contract for several companies	Manufacturing facility GMP-certified by MCC
Biovac Institute	WHO Expanded Program on Immunization: 8 vaccines procured from overseas, including DTP, measles, oral polio, BCG and *H. influenzae* B. Manufacture of hepatitis B vaccine using recombinant HBsAg vaccine obtained from Heber Biotech.	Combination pentavalent DPT + HepB + Hib vaccine in one vial. Plans to make first clinical trial material in 2009.	Plans to obtain GMP certification from MCC and South African Pharmacy Council for Port Elizabeth formulation & filling facility, with WHO prequalification in the longer term
Cape Kingdom	Five dietary supplements based on oil extracted from South African herb buchu combined with other essential oils. Buchu Force Antiinflammatory Gel (buchu oil, carbopol ultrez-10 polymer, glycereth-26, polysorbate 20, triethanolamine, diazolidinylurea and parabens) and 3 capsules: BuchuLife Antiinflammatory Capsules (5 mg buchu oil, 370 mg salmon oil); BuchuLife Pain Relief (10 mg buchu oil, 365 mg salmon oil) and UTI Relief (10 mg buchu oil, 365 mg flaxseed oil).	Developing new delivery vehicles: nasal spray, eardrops and asthma pump for pediatric use; suppository, pessary and vaginal cream for adult use	None
Disa Vascular	For both local and foreign markets: ChromoFlex stent (cobalt chromium alloy), Explorer II (PTCA balloon catheter), Trailblazer (diagnostic catheter) and angiography accessories. Radi products (intravascular sensors and homeostasis management) for South African market.	Stellium DES (cobalt-chromium stent coated with a biodegradable polymer infused with anti-restenosis drug paclitaxel) in clinical trials in South Africa	ISO 9001: 2000 and ISO EN ISO 13485:2000 certified with a full manufacturing capability including a ISO Class 7 clean room. ChromoFlex received European approval in 2004 and approval in South Africa in 2000
Elevation Biotech	None	Seven-amino-acid peptide that binds HIV gp120, blocking viral entry to T cells. Also screening to identify peptide inhibitors of HIV interaction with CD4 receptor or HIV peptide epitopes for use in immunization strategies. Developing diagnostic assays to determine chemokine CXC motif receptor-4 and CC motif receptor-5 HIV co-receptor usage.	Will apply for South African National Accreditation System accreditation for GLP in 2009

(continued)

Table 1 (continued)

Company or organization	Products on the market	Products under development	National or international quality certification
Kapa Biosystems	Research-grade DNA polymerases and nucleotides.	New enzymes through directed evolution and bioprospecting platforms	None
National Bioproducts Institute (NBI)	Human plasma–derived therapeutic proteins: lyophilized human plasma, human albumin, coagulation factors VIII and IX for hemophilia A and B, and various immunoglobulins. Diagnostics: Rapidtest Rh (Rh_o antigen immunodiagnostic) and mouse monoclonal antibodies for ELISA or immunochromatographic tests for infectious agents. Contract manufacture: recombinant proteins in *Escherichia coli* or *Saccharomycescerevisiae*. Clinical contract services: custom production of monoclonal antibodies; mouse colonies. Drug information center service staffed by pharmacists.	Human monoclonal antibodies to *M. tuberculosis* and mouse monoclonal antibodies to *T. brucei gambiense* (African sleeping sickness)	GMP-certified by MCC
Synexa Life Sciences	Leptomycin B, actinomycin D, brefeldin A, ionomycin calcium salt, ionomycin free acid, lactacystin, staurosporine, wortmannin. Contract research: lead activity screening, efficacy testing for dietary supplements and herbal remedies, pesticide residue screening for fruit exporters. Clinical services: clinical trial support in immunology and infectious disease (biomarker analysis, pharmacogenetics, analytical testing and interpretation).	Quorus Bioreactor (novel disposable, hollow fiber bioreactor for microbial and mammalian cell culture). In its final testing stage; will be commercially available in 2009.	ISO 17025 in Medical Testing Laboratory
Vision Biotech	Immunochromatographic (lateral flow) diagnostic tests using colloidal gold as a detection reagent: Pf malaria test (to detect *P. falciparum* histidine-rich protein-2), Combo Pf/Pan Aldolase test (to detect *P. falciparum* and *Plasmodium* spp. lactate dehydrogenases), Combo Pf/Pan Aldolase (to detect *P. falciparum* and *Plasmodium* spp. lactate dehydrogenases), Hepatitis (HBsAg), Syphilis, HIV Rapid (HIV1/HIV2 strains single line), HIV Rapid (dual line detection of HIV1/HIV2), Pregnancy bHCG Rapid. Contract manufacture of diagnostics.	Schistosomiasis, dengue, trypanosomiasis and tuberculosis rapid tests	ISO 13485:2003 certified and Gold CE marked

Service Companies

Company	Services offered and technological capabilities	Products or services in development	National and international quality certification
African Clinical Research Organization (ARCO)	Clinical research: phase 1 to phase 4 clinical trials, including safety monitoring, protocol writing, project management, data management and monitoring. Preclinical consulting, clinical trial site development, GCP training, CRA training.	Education, public awareness, clinical trial site development, training of doctors who want to be involved in clinical trials. Plans to extend local CRA training courses to other parts of Africa.	Clinical trials conducted under General Regulations made in terms of the Medicines and Related Substances Act, 1965 Act No. 101
Gknowmix	Genetic testing service and provision of comprehensive reports for multigene cardiovascular disease screen, in association with the University of Stellenbosch and private pathology laboratories. Cardiovascular GeneScreen (genetic test for 8 defects in the low density lipoprotein receptor gene and 12 mutations in 10 different genes involved in lipid metabolism, folate metabolism, blood clotting and iron overload), exclusive South African distributor of Agendia's MammaPrint test (breast cancer prognostic test based on expression of 70 specific genes compared to reference expression profiles), Wellness GeneScreen (nondiagnostic genetic test for 15 mutations in genes involved in lipid metabolism, folate metabolism, blood clotting, iron metabolism, inflammation, oxidative stress, detoxification of carcinogens and estrogen exposure).	Multiple sclerosis GeneScreen; enhancement of online genetic testing service delivery system, which integrates clinical indicators, pathology and lifestyle factors, operational since May 2008	
Veritrial	Clinical research: provides phase 2b to phase 4 clinical trial management for local and international biotech and pharmaceutical companies. Database in excess of 80,000 people, allowing for rapid recruitment.	None stated	Staff all GCP certified

ACE, angiotensin-converting enzyme; BCG, bacille Calmette-Guérin; βHCG, β-human chorionic gonadotropin; BMP, bone morphogenetic protein; CRA, clinical research associate; dNTP, deoxyribonucleotide triphosphate; DPT, diphtheria, pertussis and tetanus; ELISA, enzyme-linked immunosorbent assay; GMP, good manufacturing practices; GCP, good clinical practices; GLP, good laboratory practice; MHRG; Medicines and Healthcare Regulatory Agency; OBM, Osteogenic Bone Matrix; PIC/P, Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme; PTCA, percutaneous transluminal coronary angioplasty.

pricing the protein substantially lower than competitors. According to Cyril Donninger, Bioclones' former CEO and founder, biogenerics are a significant opportunity for the company: "I believe we have an obligation to make these modern biotech products in the country, in rands, so that we can offer them at a much more affordable price. We are interested in those products that can play a role in the treatment of many of the conditions you find in Africa…but we are also conscious of the fact that we have big world markets out there; it would be stupid not to be. It's a combination of these things which we consider to be important."

Therapeutics. The potential for South African companies to develop new therapeutics that address local problems is highlighted by three recent R&D startups, all with a focus on infectious disease. iThemba Pharmaceuticals (Johannesburg), a venture founded by Dennis Liotta (who discovered Emtriva (emtricitabine) and 3TC (lamivudine), among others) and several scientific colleagues from around the world, has recently received R30 million ($3.6 million) in financing from the BRICs Lifelab and BioPad to add to the founders' private investment. Through a license agreement, iThemba has access to the comprehensive compound library at Emory University in Atlanta, which it is screening for activity against local strains of tuberculosis and HIV. Ultimately, it will seek to outlicense or co-develop new chemical entities after positive proof-of-concept. Emory has also licensed to iThemba rights to a more efficient process for manufacturing generic versions of the HIV reverse transcriptase inhibitor Ziagen (abacavir). In a recent move, iThemba will partner in the development of any lead candidates resulting from a collaboration between US biotech Chimerix (Durham, North Carolina, USA) and the Medicines for Malaria Venture public–private partnership (Geneva), which aims to screen Chimerix's chemical library for compounds with activity against malaria. iThemba has emphasized the importance of attracting the best global talent to move the venture forward; Rebanta Bandyopadhyay, previously a director at Dr. Reddy's Laboratories (Hyderabad, India), recently took the post of CSO.

Elsewhere in Johannesburg, both Arvir Technologies and Elevation Biotech aim to commercialize local research in the HIV field. Arvir hopes to start building local capacity in antiretroviral active pharmaceutical ingredient (API) production through a new process technology developed by the Council for Scientific and Industrial Research (CSIR; Pretoria). The process involves the production of thymidine, a precursor to many antiretroviral drugs, such as stavudine and azidothymidine, from 5-methyluridine. It is not only cheaper than existing chemical methods but also reduces the need for environmentally harmful organic solvents. Dave Walwyn, CEO of Arvir, explains the importance of the venture: "We have a trade imbalance of about 8 billion rand a year in pharmaceuticals, and we make very few APIs in this country. They're mostly all imported. Given the number of people we hope to have on antiretrovirals by 2011—1.2 million—that's just nonsense. So that's the whole challenge for Arvir, to somehow find a way in which it can support that procurement in a beneficial and cost-effective way." The company also has three plant-derived lead compounds in development, which have *in vitro* efficacy against HIV and were originally identified by CSIR's bioprospecting program.

Staff assembling affordable point-of-care diagnostics at Vision Biotech (Cape Town).

Box 1 Case study: the Biovac Institute

The Biovac Institute is the only vaccine manufacturer in sub-Saharan Africa and a public–private partnership between the Biovac Consortium (a consortium of four local and international shareholders) and the South African Department of Health. Established in 2003, Biovac was charged with restructuring and upgrading the state vaccine assets to ensure domestic capacity in vaccine production, as well as to develop R&D capability and a local skills base to respond to future local and regional vaccine needs. Biovac supplies all eight of the government's Extended Program of Immunization vaccines at competitive prices, either importing finished vaccines from abroad or formulating and filling imported antigen concentrates locally.

Adopting a backwards-integration strategy, Biovac has established a cold-chain distribution network throughout South Africa and the rest of southern Africa, supplying vaccines to Namibia, Botswana and Swaziland. Further capacity includes a GMP formulation and filling center in Port Elizabeth and a new quality control facility built to MCC and WHO standards that can support world-class vaccine manufacture. The formulation and filling of HBsAg vaccine, using bulk recombinant antigen supplied by Cuba's Heber Biotech (Havana) began in 2008 and represents the first new vaccine to be made in sub-Saharan Africa since 2001.

Through a strong network of academic and industry partners, Biovac is also working to build its future vaccine pipeline, starting with combination vaccines. In development is the pentavalent DPT + HepB + Hib vaccine as a single liquid dose, which will make a considerable difference to the ease of vaccine delivery. The necessary technology platform (polysaccharide conjugation) was established with input from Heber Biotech and Bionet (Bangkok, Thailand), which transferred technology and helped in training of some of Biovac's 65 personnel. A recent alliance with the Istituto Superiore di Sanità (part of the Italian National Health Service) in the production of clinical trial material for an HIV vaccine represents a further step in Biovac's development as an important local and regional vaccine presence.

Box 2 Case study: Bioclones

Founded by Cyril Donninger in 1982 as a joint venture with South African Druggists (Sandton), Bioclones is the oldest biotech company in South Africa and focuses on the research, development and production of biologics and other experimental therapeutics. Bioclones spent its initial 6 years focusing on the development of advanced diagnostics reagents and holds several patents in this area in Europe and elsewhere. Since 1989, its core business has been the development of recombinant medicines, its main product being human erythropoietin, a hormone used to treat anemia caused by chronic renal failure or chemotherapy. Bioclones' EPO product, Repotin (epoetin-α), is the first EPO to be derived from baby hamster kidney cells and is manufactured at the company's GMP-approved facilities near Pretoria. Local manufacture enables competitive pricing, which has allowed Bioclones to obtain part of the state tender (government contract) for EPO for the past 9 years. With the expiration of key EPO patents held by Amgen (Thousand Oaks, California, USA) and Kirin (Tokyo), Bioclones now also has the opportunity to enter world markets.

Bioclones' patent portfolio covers several other experimental therapeutics and vaccines. The company is developing technology to isolate, grow, pulse and mature dendritic cells with a view to developing dendritic cell vaccines, and it is now looking for GMP facilities to take these products into clinical trial. Another part of the company's IP portfolio covers oral vaccines comprising thermally stable retro-inverso peptide analogs of antigens (constructed by assembling D-amino acids in reverse order to the L-amino acid order in the parent peptide). These offer considerable potential in the African context, where the need to refrigerate current vaccines is a principal barrier to successful vaccination programs. Bioclones also has an array of strategic partnerships, both with university departments and with overseas business.

Spun out of research from the University of Witwatersrand and the National Health Laboratory Service (Johannesburg), Elevation Biotech is investigating peptides that inhibit HIV entry into cells and has recently received a grant from the International Aids Vaccine Initiative (New York) for the development and testing of new vaccine antigens that elicit broadly neutralizing antibodies to HIV. Elevation Biotech also has several biochemical *in vitro* assays to detect a compound's ability to block viral entry. With commercial partners, Elevation is exploring the possibility of developing peptide-based microbicides and is seeking funding to investigate a new method of screening patients' HIV virus co-receptor tropism.

One notable company working in therapeutics that was omitted because of unavailability for interview at the time of our study is Shimoda Biotechnology (Plettenburg Bay). Shimoda is one of the oldest and most successful South African health biotech companies and focuses on proprietary drug delivery systems and new therapeutics. It was the first South African biotech company to be acquired by a foreign company; in April 2008, Abraxis Bioscience of Los Angeles bought Shimoda, along with its subsidiary Platco Technologies.

Nutraceuticals. Several of the BRICs and incubators have supported ventures in the nutraceutical field—foods, food constituents or dietary supplements that provide medicinal or health 'benefits'. Described by one interviewee as 'low-hanging fruit', nutraceuticals have the potential to generate early commercial successes because of the shorter path to market. Although not studied as part of this analysis, an example is Sandton-based Natural Carotenoids South Africa, a CSIR spinoff based on the extraction of natural carotenoids (a source of vitamin A and antioxidants) from algae. Natural Carotenoids South Africa now produces a range of products under GMP conditions, including suspensions, crystals and powders for the nutraceutical and food industries. In Pretoria, Biomox Pharmaceuticals manufactures Bio Boost, an 'immunosupportive' dietary supplement containing L-methionine, magnesium, vitamin B6, vitamin B12 and folic acid.

Some companies are attempting to bring increased scientific rigor to the complementary health product field, motivated in part by an attractive potential export market. Cape Kingdom (Cape Town), for example, which manufactures five products based on the herb buchu, one of South Africa's best-known healing plants, is carrying out clinical trials to validate the anti-inflammatory properties and has contracted out work on the isolation and chemical characterization of buchu's active ingredient.

Reagents, diagnostics and medical devices. Reagent suppliers, diagnostics and medical devices are all active areas of innovation in South Africa because of their lower barriers to commercial entry. Product development in all of these areas is subject to a more lenient regulatory regime and shorter investment timelines than therapeutics or vaccines.

US-owned Kapa Biosystems (Cape Town) is applying directed evolution to optimize the enzymes used in research tools, with a focus on thermostable DNA-manipulating enzymes, particularly DNA polymerases and ligases. Kapa is also developing several new enzyme-based products using bioprospecting platforms. The company launched a variety of enzymes in 2007, with a focus on international markets. The business strategy takes advantage of the fact that several key directed evolution approaches and the products derived from them, though patented in Europe and the United States, are not covered by patents in South Africa.

Elsewhere, the Durban-based not-for-profit National Bioproducts Institute (NBI; **Box 3**) has built its core business around supplying plasma-derived products and also has a longstanding biotech division that focuses on infectious disease. Products include recombinant proteins for use as immunogens to produce monoclonal or polyclonal antibodies or as antigens in diagnostic tests, as well as mouse monoclonal antibodies for use in immunodiagnostics, such as enzyme-linked immunosorbent assays (ELISA) and immunochromatographic tests. In collaboration with the University of KwaZulu-Natal Medical School, NBI has developed a rapid bedside test to determine rhesus status that is now used in public hospitals in all nine South African provinces. With close links to the South African National Blood Service, NBI also makes ELISA tests for the in-house screening of plasma samples from blood donors for antibodies to hepatitis B virus, *Clostridium tetani* (tetanus), rabies virus and varicella zoster virus. NBI is now developing a human monoclonal antibody to *Mycobacterium tuberculosis* and a mouse monoclonal antibody to *Trypanosoma brucei gambiense* (African sleeping sickness) to develop new diagnostic tests. For both tuberculosis and African sleeping sickness, early diagnosis and treatment is associated with better patient outcome. The inadequacies of current tuberculosis tests are well known, and at present, it is thought that only 10% of patients with African sleeping sickness are accurately diagnosed[15].

In the area of diagnostics, Vision Biotech (Cape Town) develops and contract manufactures point-of-care diagnostic tests, with a focus on affordability and high reliability in African field conditions. Operating since 1995, Vision has developed 15 types of Gold CE-marked test over the past two years (CE marking indicates conformity to the legal

requirements for the manufacture of *in vitro* diagnostic medical devices for sale in the European Economic Area), all but one based on lateral-flow (immunochromatographic strip) technology and preferentially using colloidal gold as a detection reagent (**Table 1**). Most of these diagnostics focus on infectious diseases, such as HIV, tuberculosis and malaria. Indeed, Vision is the second biggest manufacturer of malaria tests worldwide, making 8–10 million malaria tests each year and supplying the WHO's 'Pf malaria' test (a rapid immunodiagnostic test for *Plasmodium falciparum* histidine-rich protein 2 antigen), a 'Combo Pf/Pan ldh' test (immunodiagnostic test against *P. falciparum* and other *Plasmodium* spp. lactate dehydrogenases) and a 'Combo Pf/Pan aldolase' test (an immunodiagnostic test against both *P. falciparum* and other *Plasmodium* spp. aldolases). The Pf malaria kit is available for $0.50 per test, whereas the combination tests are available at $0.65 per test. Although reaching rural areas is challenging, Vision has built a robust distribution network for its diagnostics in southern Africa. Nick Borain, Vision's CEO, emphasizes the importance of affordability in accessing African markets: "We really do satisfy the sort of market requirements here, in sub-Saharan Africa, which are very much price driven. Obviously quality and stability are very important, but without the right prices, it's just a no-go."

With a history of excellence in biomedical engineering and clinical expertise in heart disease, medical devices are also a natural focus for South African health biotech ventures. Disa Vascular (Cape Town; **Box 4**) produces several niche products for treatment of coronary and peripheral artery disease, including coronary stents and diagnostic catheters. Disa's ChromoFlex coronary stent is made from a special cobalt chromium alloy and received European CE mark approval in 2004. In the pipeline is its Stellium drug-eluting stent—a third-generation device designed to overcome late stent thrombosis—now in human trials in South Africa. With substantial local demand for, and expertise in, device technologies, South Africa has proven a useful incubator for medtech businesses, which can also tap into global markets.

One challenge for South Africa's health biotech companies is to make connections that can help them compete in a global industry.

Altis Biologics (Johannesburg) is another R&D-focused device company; it has developed a method for the high-yield extraction of a cocktail of bone morphogenetic proteins (BMPs) from natural sources through fractionation of total bone protein (extracted by urea treatment) into a low-molecular-weight portion (enriched for BMPs), which is then separated chromatographically. BMPs are members of the transforming growth factor-β superfamily of morphogenic proteins capable of inducing osteoclast formation in mammals and are thus of interest in such applications as complicated fractures, bone loss and periodontal problems. Altis is commercializing its technology through a partnership with Tshwane University of Technology and Bone SA, a Johannesburg nonprofit that processes and distributes human allograft bone and soft tissues for orthopedic and other types of surgery. Since 2005, Bone SA has marketed Endogen IVT, demineralized human bone matrix produced using Altis's fractionation method. Altis is also developing BMP-rich Osteogenic Bone Matrix (OBM), a xenotransplantation product derived from bone processed from pathogen-free pigs, as an implant material and delivery system intended as an alternative to traditional bone graft procedures. The company intends to launch the product first in South Africa and then obtain a CE mark approval. Testing of OBM's effectiveness in bone induction is expected to be completed in 2009.

Synexa Life Sciences (Cape Town, **Box 5**) has developed a bioreactor that increases the productivity of microbial and mammalian cell culture. The bioreactor is based on hollow-fiber membrane fermenters that concentrate biomass

Box 3 Case study: National Bioproducts Institute

Founded in 1994, the National Bioproducts Institute (NBI) aims to meet South Africa's needs for plasma-derived medicines, building a sustainable business model supported by public funding from a collaboration with South Africa's Department of Health and Blood Transfusion Services. NBI was previously a division of the South African National Blood Service (SANBS; Johannesburg), and between 1994 and 2004 it was known as the Natal Bioproducts Institute. In 2000, a newly defined Biotechnology Division was established, which brought together existing local expertise in immunochemistry and ELISA kit production.

NBI makes a range of products predominantly for the South African market, with a limited number of exports. Pharmaceutical products include human plasma (lyophilized), human albumin solutions, coagulation factors used to treat the hereditary bleeding disorders of hemophilias A and B and immunoglobulins. The Biotechnology Division produces monoclonal antibody reagents for use in the manufacture of rapid bedside testing systems as well as a rapid bedside tests to determine the rhesus status of patients and ELISA tests for the in-house screening of plasma samples from local SANBS blood donors for antibodies to hepatitis B virus, *Clostridium tetani*, rabies virus and varicella zoster virus.

NBI employs 150 staff (126 permanent) at its premises in Pinetown, Durban, 15 of whom focus on biotech, and it has supported the education and advanced training of several staff members. NBI is self-financing, with an annual turnover of approximately $28 million (11% of which comes from exports) and R&D spendings of 2.2% of revenues. NBI has forged several partnerships: it is collaborating with PATH, FIND and WHO to develop positive controls for rapid malaria tests, and it is also working locally with the Blood Transfusion Service of Namibia, Windhoek with a view to processing plasma of acceptable quality from Namibia.

In a recent development, NBI is also collaborating with the Lifelab BRIC to transfer some of NBI's expertise and develop a new platform for making monoclonal antibodies using hollow fiber technology. In addition, the institute is providing staff training and scientific oversight of the project.

Box 4 Case study: Disa Vascular

Disa Vascular is an R&D-focused medical devices company based in Cape Town. It was founded in 1998 by Gregory Starke, an expert in computational mechanics at the University of Cape Town, who wished to apply his work on orthopedic implant design and vascular grafts to the development of vascular stents for the treatment of coronary and peripheral artery disease. Disa's first stent was implanted at Groote Schuur Hospital (Cape Town) in 2000—a short development timeline due in part to the lack of medical devices regulation in South Africa—and received European approval that same year.

This achievement attracted a small investment ($300,000) from angel investors to add to initial funding from founders. In 2002, Disa captured the attention of the Bioventures venture capital fund, which added $1 million in equity. With this resource, Disa began building and diversifying its brand, and by 2004 it had developed the Chromoflex stent, a cobalt-chromium stent containing several novel features: stronger material, improved flexibility and thinner struts that reduce the probability of restenosis (abnormal narrowing of arteries). Since then, Disa has attracted further funding from several sources, including $1 million in investment from Cape Biotech for its Stellium drug-eluting stent now in development, which is designed to overcome issues of late stent thrombosis associated with first-generation stents. On the basis of favorable animal studies, Disa is conducting domestic clinical trials of this product.

With a current product portfolio including coronary stents, balloon catheters for percutaneous transluminal coronary angioplasty, diagnostic catheters and angiography accessories, Disa generates an annual revenue of ~$1.8 million, 50% of which is from exports to Europe, South America and Asia. The company is investing in marketing, recruitment and a more extensive R&D capacity, as well as the establishment of a production facility on-site. Last year, Disa broke new ground for a South African biotech by securing R4.5 million ($570,000) in investment from a Swiss company, potentially strengthening its European presence.

Disa Vascular's CEO Greg Starke at his offices in Cape Town. Disa's vascular stents are sold locally and internationally and show the potential for South African innovation in medical devices.

into layered biofilms, reducing cell shear due to the culture medium. Synexa also has a small bioprospecting program focused on isolating biologically active molecules from new microbial sources and offers contract services, such as biological activity screening and chemical characterization of natural compounds.

Contract services. The service industry in South Africa is relatively large and ranges from contract R&D to clinical trials to manufacturing. Clinical trials in particular have traditionally been strong in South Africa, and the local clinical research industry has about 3% of the global market of $10 billion[16]. Reasons for its success include the large and varied disease burden (covering a range of indications, from infectious diseases to cancer and central nervous system diseases), the large number of drug-naive patients, high-quality hospitals and well-developed clinical trial regulation and ethics approval processes. South Africa is English-speaking and within the same time zone as Europe, which has also encouraged international work, particularly with the UK. South Africa follows the International Conference on Harmonisation (ICH) good clinical practice (GCP) guidelines in addition to South African GCP regulations based on ICH with locally applicable clauses, such as those pertaining to vulnerable populations and HIV trials.

Although contract services are dominated by multinational companies, local ones operating in this space include Veritrial (Johannesburg), which has a focus on studies from phase 2b to phase 4, and the African Clinical Research Organisation (ACRO; Johannesburg), which is a joint venture with Batswadi Pharmaceuticals (Johannesburg). ACRO is a private nonprofit focused on infectious diseases and on donor-driven work and is the only full-service clinical trials company in South Africa. In an effort to support local biotech SMEs, ACRO is offering local ventures favorable rates, which could result in cost savings of up to 40%.

Of the companies interviewed, several are using contract manufacturing to subsidize R&D; these include services for the manufacture of natural products (Biomox), diagnostics (Vision Biotech) and monoclonal antibodies (NBI), as well as small molecule and specialized microbially derived products (Synexa Life Sciences; see **Box 5**) with several of them under GMP conditions (**Table 1**). In the area of natural products, Biomox has formed a partnership with the University of Pretoria's PhytoMedicines Division, which specializes in the R&D of herbal extracts, to create a subsidiary, Bioextracts (Pretoria), that conducts contract development and manufacturing work, its most successful product being a high-quality grapeseed extract developed for Merck South Africa (Modderfontein).

Other niche services include Lazaron Biotechnologies (Cape Town), which has established the first stem-cell bank in Africa, focusing on umbilical cord blood banking. The bank can store 1,500–5,500 specimen samples per year at a cost of R6,500 each. And in the genetic testing area, Gknowmix (Cape Town) is developing an online system that integrates clinical, pathology and lifestyle factors and results into 'comprehensive, quality controlled reports' for patients, offered through private pathology laboratories. The company offers gene tests for breast cancer (*BRCA1* and *BRCA2* profiling, as well as exclusive access to Agendia's (Amsterdam) MammaPrint test) and for cardiovascular disease (8 mutations in low-density lipoprotein receptor gene and 12 mutations in 10 undisclosed genes involved in lipid metabolism, folate metabolism, blood clotting and iron overload).

Partnerships

Partnerships are key to accessing the new technologies, markets and skills that make growth possible. Although most of the South African health biotech companies interviewed were involved in at least one domestic or international partnership, many highlighted the

difficulty of forming collaborations. Reasons for this included geographic isolation, the small size of the local industry, lack of knowledge overseas about private sector activity in South Africa and, particularly, the perceived lack of credibility of 'made in Africa' products.

Most of the companies interviewed had domestic partnerships with universities and research institutions. These varied in terms of commitment and duration, some being ongoing research partnerships (for example, when the company itself was a spinoff) and some based on contract work in specific areas such as clinical trials (**Table 2**). For those companies based in an academic environment, such as AngioDesign, Elevation Biotech and Altis Biologics, most had links with the institution beyond simply using the infrastructure. Personal connections underpinned many of the foreign research collaborations, arising either from expatriates who have returned to South Africa or foreigners who left the country after spending time in South Africa (**Table 2**). In general, the university–industry relationship brought with it difficulties as well as advantages. Companies frequently cited frustrations around lack of commercial knowledge in universities, prolonged IP negotiations and unrealistic expectations of success and of revenue.

Domestic private sector collaborations between companies are almost nonexistent in South Africa, partly because of the lack of critical mass in any one area. The absence of a research-based pharmaceutical industry is also a clear limiting factor. International company–company partnerships, usually with European companies, were much more common, and South African biotechs put a lot of energy into establishing these relationships. For a sector that needs to reach global markets to grow, such partnerships are vital, particularly for accessing necessary technologies and markets and raising local companies' international and domestic reputation (**Table 3**). Common alliances cited by companies were in the areas of manufacturing, distribution and animal studies, the last of these due to the dearth of certified animal facilities in South Africa.

Alliances with other developing-country companies are few but growing. A recent example is East Coast Rapid Diagnostics (Durban), a joint venture between the Lifelab BRIC and the Tulip group of Goa, India. East Coast Diagnostics is commercializing rapid immunodiagnostic kits for pregnancy and infectious diseases developed by the publicly funded Institute of Diagnostics Research (Durban), and it is also developing a range of urine dip-stick immunodiagnostics. Other areas of partnership identified in our survey were links between companies and foreign not-for-profit organizations working in health. NBI, for example, is now working with PATH (Seattle), FIND (Foundation for Innovative Diagnostics; Geneva) and WHO to develop positive controls for rapid malaria tests.

Some companies, such as Biovac, have positioned partnerships to be central to their operations, pursuing several 'technology partnerships' with overseas companies to enable technology transfer as well as skills transfer and training. Biovac has led the way in South–South partnerships, making links with other Southern companies such as Heber Biotech (Havana, Cuba), BioFarma (Bandung, Indonesia) and BionetAsia (Bangkok, Thailand), which is helping to transfer a new vaccine technology platform to develop Biovac's future pipeline. Patrick Tippoo, R&D manager at the Biovac Institute, emphasizes that choosing the right kind of partnership is important in a resource-strapped environment: "We've positioned ourselves very carefully. Because of our limited resources, we can't do everything on our own, so our strategy is to embrace projects or opportunities that are closer to commercialization, requiring a GMP environment for manufacture of clinical trial material…we partner with people who can provide us at least with a proof of concept before we have to jump in and take the risk in terms of time, effort and investment." He also highlights the opportunities that working in South Africa presents: "We are in unique position because we have a mix of a first-world and third-world set-up. So while we may be considered to be a third-world country, much of our infrastructure is first world. This presents us with real opportunities in terms of overseas institutions that are compelled to partner with institutions in developing nations to access some funding for projects."

Box 5 Case study: Synexa Life Sciences

Founded in 2001, Synexa Life Sciences is a Cape Town–based biotech company with four main areas of commercial interest: the development of new bioprocess technologies, the production of biologically interesting small molecules, the provision of specialized bioanalytical services and bioprospecting.

Motivated to create a sustainable biotech company, with a focus on innovative bioprocessing technology, Synexa's founders are an interdisciplinary team with expertise in management, medicine and immunology. Initial funding from founding shareholders was supported in 2003 by financing of R10 million ($1.6 million) from local venture capital fund Bioventures and the Industrial Development Corporation of South Africa. A second round of financing in late 2003 raised another R11 million ($1.8 million) from the Cape Biotech Trust.

Synexa's proprietary technology is the Quorus Bioreactor, which provides an alternative to traditional submerged culture bioreactors used for the manufacture of natural and recombinant products. The bioreactor contains hollow capillary membranes that encourage the growth of microbial biofilms by establishing a nutrient gradient supporting optimal growth and preventing culture shear. Designed for in-house use by biotech or pharma companies, the reactor can be scaled up from lab to pilot-scale capacity. Fully developed as a disposable technology, the Quorus is in final testing and will be commercially available in 2009.

Contract manufacture and development is another strong element of Synexa's business model. This includes the manufacture of microbially derived secondary metabolites, such as ionomycin and leptomycin B, as well as the production of recombinant proteins.

The company's bioanalytical services division offers a wide range of biological and chemical analyses, including clinical trials analyses (biomarker analysis, pharmacogenetics, analytical testing and interpretation) at an ISO-accredited laboratory. Synexa also offers biological efficacy testing of complementary medicines. More recently, the company has offered contract bioprospecting projects that focus on isolating new microbial sources, including endophytes from South Africa's rich flora.

Based at the medical campus of Stellenbosch University, Synexa has 25 full-time staff, including 14 MScs and PhDs. The company's business model combines revenue-generating service activities, contract production and pure R&D, enabling a degree of commercial sustainability.

Financial environment and business models

Financing for biotech ventures in South Africa is still strongly government led, with the BRICs and incubators at the forefront. The BRICs have been actively investing since 2003; however, a budget of only R450 million ($58 million) over three years (2004–2007) has necessitated that they be fairly cautious in their investment choices. At present, the two BRICs focused on human health, Cape Biotech and Lifelab,

support ~16 projects in this area through a combination of equity stakes and loans. As well as early-stage ventures, the BRICs are charged with investing in technologies that can be used by the business and academic community and, in the longer term, stimulate private sector activity in high-tech areas. Examples of these are the Centre for Proteomic and Genomics Research (Cape Town), a high-throughput research and analytical services facility; the National Genomics Platform (Durban); and the Institute for Diagnostic Research (Durban).

Many of the companies interviewed in our survey had benefited from seed funding from the BRICs, and in general, company management felt that funding conditions were reasonable (**Table 4**). Issues raised included a lack of focus (that the money for investment was spread too thinly to be effective), slow turnaround times in securing grants and a short-term investment perspective. This last issue is particularly pressing now that several companies that benefited from initial BRIC funding are seeking more financing and the BRICs are not sufficiently capitalized to scale up their investments. Other sources of government funds most frequently accessed were the Innovation Fund, an instrument of the Department of Science and Technology to fund end-stage research across a wide range of sectors; the Industrial Development Corporation (IDC), a national development financing institution supporting competitive industries; and the Support Programme for Industrial Innovation (SPII), administered by the IDC, which was designed to promote technology development in the manufacturing industries. Again, these offer a combination of grants, equity stakes, loans and performance-linked loans, among other forms of financing. There was a less positive response to some of these funds, with companies feeling that conditions attached were onerous and frequently worked against SMEs. The Innovation Fund's Patent Support Fund, for example, which will match funding for patent applications on a 50:50 basis, will also assume IP if it is not commercialized within a given timeline, which companies saw as a major disincentive. Some interviewees felt

Table 2 Alliances and collaborations between companies interviewed and domestic organizations

Company	South African alliances and objectives
ACRO	None
Altis Biologics	Outlicenses BMP technology to Bone SA. Sublicenses manufacture of all human-derived products sold by Bone SA to Tshwane University of Technology. Collaborates with University of Pretoria on clinical trials related to use of OBM in dental field, with Medical University of Southern Africa on other uses, and with CSIR regarding new osteoinductive delivery systems. Works with good farming practice producers of specific pathogen-free pigs
AngioDesign	Collaborates with Department of Chemistry, University of Cape Town and with the University of Witwatersrand for animal trials of new domain-selective angiotensin-converting enzyme inhibitors.
Arvir Technologies	Collaborates with the CSIR on research into process technology (cost-efficient method to manufacture antiretroviral APIs) and product technology (development of 3 phytopharmaceutical leads from bioprospecting program, which have been shown *in vitro* to have efficacy against HIV).
Biomox	Tshwane University of Technology provides a 1-year training course in complementary medicines and helps to conduct their clinical trials. University of Pretoria carries out human and animal research on immune-supportive supplements, including phytomedicinals.
Biovac Institute	Forms part of a public–private partnership with the South African Department of Health, incorporating the State Vaccine Institute into a commercial company. Collaborates with Bodene (Port Elizabeth) for formulation and filling of final vaccine products from overseas concentrates in dedicated Biovac suite and with University of Cape Town on human papilloma virus vaccine (ended June 2006). Advises Stellenbosch University on cholera vaccine development strategy and commercialization. Cape Biologicals (Cape Town) supplies Hib production technology.
Cape Kingdom	Contracted Synexa Life Sciences to test buchu oil *in vitro* and characterize active ingredient. Collaborates with Sports Science Institute of University of Cape Town on placebo-controlled, double-blind trial of Buchu Force gel and with the Cancer Association of South Africa (Cape Town) on observational trials. Supplies various local distributors with Cape Kingdom products.
Disa Vascular	None
Elevation Biotech	Provides consulting advice on peptide binding to Onderstepoort Veterinary Institute. CSIR Biosciences provides surface plasmon resonance testing instrument platform. Works with Batswadi Pharmaceuticals to develop microbicide based on HIV entry inhibitor molecules; links with a local peptide supplier.
Gknowmix	Has alliances with local laboratories, including Lancet Laboratories (Gauteng), Molecular Diagnostic Services (Durban) and the Pathology Research Facility (Cape Town), that carry out genetic testing and use Gknowmix's genetic knowledge integration facility.
Kapa Biosystems	None
National Bioproducts Institute	Has close links to SANBS, which supplies plasma to NBI. NBI screens donor samples from SANBS for presence of antibodies to tetanus, hepatitis B virus, rabies virus and varicella zoster virus and to establish donor panel for the supply of anti-D plasma to make South Africa self-sufficient in the manufacture of anti-D immunoglobulin, used to prevent fetal harm due to Rh(D) rhesus factor incompatibility. SANBS plans to carry out research into the carrier characteristics of *P. falciparum* in South African blood donors using an NBI-developed malaria ELISA. Collaborates with University of KwaZulu-Natal Medical School on the development and design of rapid bedside test to determine rhesus antigen status; working with Lifelab BRIC to establish the Institute of Diagnostic Research, which will develop diagnostic products for neglected diseases.
Synexa Life Sciences	None
Veritrial	Negotiating to establish new clinical trials unit with Black Empowerment partner. Objective is to implement current systems and expertise in a new environment.
Vision Biotech	Collaborates with University of Cape Town on a research project on the plant expression of chicken egg immunoglobulin (IgY) antibodies; University of Cape Town Department of Pharmacology grows malarial parasites for controls

API, active pharmaceutical ingredient; BMP, bone morphogenetic protein; BRIC, Biotechnology Regional Innovation Centre; OBM, Osteogenic Bone Matrix; SANBS, South African National Blood Service.

that there was a lack of coordination amongst these initiatives, leading to competition between funding sources for the same ventures. Others highlighted the lack of funding for SMEs to undertake R&D. Still, others felt that funding was not based on holistic thinking about the innovation chain; some product development projects were successfully completed but then did not receive further support for the critical final stage of commercialization. An underlying reason for the problems raised was a shortage of experienced staff in these organizations able to understand the biotech business environment and to provide authoritative business advice.

Private financing for biotech in South Africa remains severely limited. Several entrepreneurs have made substantial investments of their own money or have raised funds from industry associates, friends and family to overcome this problem (**Table 4**). Lack of a strong venture capital (VC) tradition in South Africa, a shortage of investors who understand the biotech sector, risk aversion and the bigger returns on investment available from competing industries, such as construction or information technology, have all been cited as reasons for the funding gap. The result is that seed and early-stage funding in South Africa is low. Second and third round funding to get a product to proof-of-concept stage is a particular problem—estimates are that for Series A (first round) funding, a typical South African SME receives $1.4 million, compared with $5 million for a company in Europe or $10 million for a US venture; for Series B (second round) funding, a typical South African company receives $2.5 million, whereas European and US companies raise $15 million or $20 million, respectively[17].

The only VC firm active in biotech in South Africa is the life sciences venture fund Bioventures, which raised a fund of R80 million ($10.3 million) in 2001 from South Africa's Industrial Development Corporation and the International Finance Corporation (Washington, DC). By 2004, Bioventures was fully vested in eight companies, including Disa Vascular, Synexa and Shimoda, with typical investments of around $750,000. However, the fund was relatively small when compared to those in other countries and its lifespan only seven years, not necessarily long enough for a company to establish itself in the biotech space. Commenting on the frustrations and opportunities of working in South Africa, where investors are relatively unfamiliar with the health biotech business, Bioventures fund manager Heather Sherwin suggests local entrepreneurs should play to the region's strengths: "I think in biotech, our strength is not in manufacturing as it is India, our strength is in R&D. You've got to be proactive and go find the good R&D and actually do something with it. It's been a problem in South Africa, where VCs expect the ideal company to walk through the door and it doesn't. You've actually got to put a management team there and develop it. We've done that and I firmly believe there's a lot more out there, it's just that it's not sitting in already perfect start-up companies." Bioventures is in the process of

Table 3 Collaborations and partnerships between companies interviewed and foreign entities

Company	International alliances and their objectives (where stated)
ACRO	None. Looking to partner with small international CROs on multicenter trials and to work with foundations or NGOs to build clinical trial site capacity across Africa.
Altis Biologics	In advanced stages of a due diligence for the licensing of the Altis BMP technology platform for the production of new human BMP-based products to biggest human tissue producer in US. Collaboration in India involving human clinical trials related to use of porcine BMP (porcine Bone Morphogenetic Protein) in dental indications; with Pentax (Tokyo, Japan) for the development of BMP and hydroxyapatite products; with large hospital in China for preclinical and clinical applications of OBM; with Rephartox (Onstwedde, The Netherlands) to conduct animal studies related to use of BMP in treating (nonsystemic) osteoporosis. Needs more financial backers to take this to the clinic.
AngioDesign	Cresset Biomolecular Discovery (Hertfordshire, UK), a small drug-discovery company, has taken a sweat equity stake in AngioDesign. Cresset uses novel technology to create a molecule field print, reflecting the electrostatic and hydrophobic fields of AngioDesign's inhibitors' structures, which they search against their database to extract new diverse compound series with similar fields, predicted to have a high probability of activity. Research contracted to both University of Bath, UK and University of Cape Town.
Arvir Technologies	None
Bioclones	None
Biomox	None
Biovac Institute	Heber Biotech provides skills transfer and training and tech transfer agreement to supply recombinant HBsAg; BioFarma supplies DTP antigen concentrate; Bionet provides input into polysaccharide conjugate platform; Statum Serum Institute (Copenhagen) supplies BCG vaccine; Sanofi Pasteur (Paris) collaborates on vaccine supply; Istituto Superiore di Sanità collaborates on manufacture of clinical trial material for HIV Tat vaccine.
Cape Kingdom	None. In negotiation with several potential partners.
Disa Vascular	Manufacture of device parts through a German company; collaborations with distributors in Europe, Asia and Brazil to market stents; animal testing through research center in Atlanta
Elevation Biotech	Contract with German supplier of peptides; collaboration with Drexel University (Philadelphia) on microbicide development
Gknowmix	Alliance with Agendia to act as South African agency for their MammaPrint service, which identifies patients with early-stage breast cancer
Kapa Biosystems	Working with a facility in Boston on sales, marketing and business development
National Bioproducts Institute	Collaborations around plasma fractionation and virus inactivation: solvent-detergent technology licensed from New York Blood Center; factor VIII manufacture processes (for heparin purification) from UK Bio Products Laboratory (Elstree, UK); and human plasma manufacturing technology from Octapharma (Vienna). Collaborative project with the Blood Transfusion Service of Namibia aiming to process plasma of acceptable quality from Namibia and partnership with PATH, FIND and WHO to develop positive controls for rapid malaria tests.
Veritrial	Contractual arrangements with several pharmaceutical companies and CROs to conduct clinical trials in South Africa on their behalf
Vision Biotech	First 5 years of Vision involved 'cross-pollination of technology' with Alchemy Laboratories (now BBInternational; Dundee, Scotland, UK); collaboration is on hold. Previous work with PATH (on malaria test).

BCG, bacille Calmette-Guérin; BMP, bone morphogenetic protein; CRO, contract research organization; DPT, diphtheria, pertussis and tetanus; FIND, Foundation for Innovative New Diagnostics; NGO, nongovernmental organization; PATH, Program for Appropriate Technology for Health.

Table 4 Financial background of companies interviewed

Company	Year founded	Public or private	Approximate annual revenues	Government grants	External private investment[a]	Approximate revenues from exports	Approximate annual R&D expenditure (% of total revenues)	Number of employees (involved in R&D)
ACRO	2007	Private	~$600,000–1,200,00 projected for first year	$1.5 million over 5 years from Lifelab BRIC	Batswadi Pharmaceuticals providing infrastructure support (human resources, finance, information technology)	None	None	6
Altis Biologics	2001	Private	$30,000 from platform licensing and $100,000 from technology management services	~$1.9 million from the Innovation Fund (Pretoria) in 2003 (interest-free, risk-based loan repayable with a maximum of 5% royalty on any future sales of OBM). Royalties will only become payable once Altis makes revenues from sales of OBM.	None	None	Four times total income. The R&D capital was raised 4 years ago.	6 (4)
AngioDesign	2003	Private	No revenue at present	None	Small grant from Sulis Foundation (Bath, UK), which provides support for the early stage commercialization of research generated by the Universities of Bath, Bristol and Southampton in the UK	None	None	NA
Arvir Technologies	2006	Private	$18,500 from contract research services by CEO; no sales as yet	~$2.5 million for 4 years from Lifelab BRIC	None	None	$650,000	1 (R&D outsourced)
Bioclones	1983	Private	Not disclosed	BRIC funding for Bioclones subsidiary Ribotech[a]	Sekunjalo Investments Limited has undisclosed investment in Bioclones	Not disclosed	Not disclosed	18
Biomox	1993	Private	~$3 million	~$1 million in unsecured shareless loan from IDC in 1993 for immunosupportive supplement	Initial funding of $1 million	Negligible	~2% on average over the past 10 years	80 (3)
Biovac Institute	2003	Public–private partnership 40% owned by the DOH, 60% owned by Biovac Consortium: 4 different shareholders (local and international)	$25 million	$1.89 million from Biovac Consortium; $378,000 from Innovation Fund for human papilloma virus project (2006) and $1.89 million from Innovation Fund for Pentavalent vaccine project (2006)	None	$2 million	2.5%	65 (16)
Cape Kingdom	2006	Private	~190,000	$1.26 million in Cape Biotech (equity)	~$5 million	Not disclosed	~$315,000	10 (2)
Disa Vascular	1998	Private	~$1.8 million	~$150,000 from 5 rounds of Competitiveness Fund (South African Department of Trade and Industry matching fund) in 2000; ~$800,000 of equity and ~$500,000 of debt from the IDC in 2004 after success of cobalt-chromium stent; $1 million from Cape Biotech for drug-eluting stent	Private investment in 2000 of $300,000; in 2002, Bioventures invested $1 million; in 2007, Lacuna Apo BioTech, which invested ~$600,000 under advisory of Swiss-based Adamant Biomedical Investments, took an equity position	$900,000 (50%)	30%	23 or 24 (3)

(continued)

Table 4 (continued)

Company	Year founded	Public or private	Approximate annual revenues	Government grants	External private investment[a]	Approximate revenues from exports	Approximate annual R&D expenditure (% of total revenues)	Number of employees (involved in R&D)
Elevation Biotech	2006	Private	No substantial revenue at present. Earned small amounts for consulting activities to local industry.	~$1.3 million from Lifelab BRIC; lab space and personnel, basic operating costs from National Health Laboratory Services and University of Witwatersrand	None	Not disclosed	~$390,000	3 full-time employees, 5 part-time employees, 2 students (9)
Gknowmix	2007	Private	~40,000	Undisclosed support from Acorn Technologies, Medical Research Council (South Africa) and SPII	None	Not disclosed	$40,000 for development of web-based genetic testing service delivery system	2 part-time (1)
Kapa Biotech	2006	Private	Not disclosed	$3.5 million in equity-based funding in 2005	$3.5 million in total from industry investors, friends family	Not disclosed	Not disclosed	22 (8)
NBI[b]	1994	Private not-for-profit	$28.2 million	Some research funded by South African Department of Science and Technology	Receives some funding from WHO and the FIND for research	$3.1 million (11%)	2.2%	150, of whom 126 are permanent; Biotech Division, 15 (5)
Synexa Life Sciences	2003	Private	$1.5 million after 2 years	$1.5 million loan from Cape Biotech in 2003; $50,000 in IDC equity funding in 2003	$750,000 in venture capital from Bioventures, South Africa in 2003	Not disclosed	~$1 million	25 full-time, 3 part-time (14)
Veritrial	1997	Private	~$190,000 per year	None	None	Not disclosed	Not disclosed	6–7
Vision Biotech	1999	Private	$5 million	None	Undisclosed; all funding private	$1 million	15%	56, of whom ~14 are core and permanent; balance on contract rotation (6)

BRIC, Biotechnology Regional Innovation Centre; DOH, Department of Health; FIND, Foundation for Innovative New Diagnostics; IDC, Industrial Development Corporation; NA, not applicable; OBM, Osteogenic Bone Matrix; SPII, Support Programme for Industrial Innovation.

[a]Ribotech (Cape Town) is a subsidiary of Bioclones involved with biopolymer production at a pilot production facility that complies with GMP requirements. [b]NBI was previously a division of the Natal Blood Transfusion Service (now the South African National Blood Service), since the early 1970s. Between 1994 and 2004, NBI was known as Natal Bioproducts Institute.

raising a follow-on life sciences fund, although, according to Sherwin, this is proving difficult.

Although South Africa has the well-regarded Johannesburg Stock Exchange (JSE), as yet, there are no biotech ventures listed, and it is widely agreed that listing on the JSE is not a viable option for biotech companies at present, thus limiting potential exit strategies. The small number of companies that have considered going public (though none has yet done so) are looking at European or US exchanges; as one CEO said, "We would need to step outside the South African capital markets, definitely, because we'll never get good value in this country."

What this amounts to is a severely constrained funding environment that limits exits for investors and poses a considerable risk to the long-term success of the biotech sector. With the average biotech company requiring multiple rounds of financing before it is sustainable, several fledgling South African companies are facing the 'valley of death' with no means of support. Government funds, though welcome, are limited, and South Africa's investment community is underdeveloped when it comes to investing in health technologies. Furthermore, with only one venture capital fund active in life sciences, there is no network to syndicate investments and thus share risks across investors. Without a change in this funding picture, the efforts that the government has made so far in stimulating biotech activity threaten to be undermined.

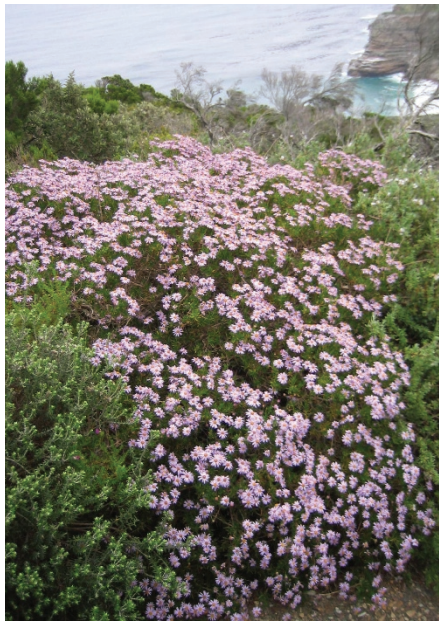
SMEs in South Africa have adopted several business models to enable survival in a difficult, resource-strapped environment, all with a focus on cost reduction. There was a broad consensus that US or European biotech business models were not realistic or relevant in South Africa, where the focus is on sustainability and a company's worth is based largely on revenue. Nor would that model necessarily be useful in nurturing the industry: as one interviewee put it, "In the US, the biotech industry is 3,000 small biotechs and they're all quite focused on a particular molecule or a particular drug target. As an industry that model works quite well because the Darwinian forces will make sure that the ones that are properly focused will succeed, and the others will fail. When you've got only a small number of companies like South Africa you can't afford that, because if enough of those fail you kill the industry. So we can't afford to do that here. The model's got to be different; we've got to be self-sustaining."

Several companies have therefore adopted a 'hybrid' business model, pursuing a service

or product element early in their lifecycle to generate revenue and help fund innovative activities. Synexa LifeSciences, for example (**Box 5**), offers specialist contract production and clinical trial support in immunology and infectious disease to support its more R&D-intensive work. The company looks for extra funding to fast-track special opportunities (for example, bioprospecting) or brings in partners to help grow parts of its business (for example, clinical trials). The NBI also uses revenue from sales of its malaria antibodies to support R&D.

Another common strategy is for companies to base themselves in academic environments for bootstrapping purposes, minimizing overheads and sometimes sharing key investments. Altis Biologics is based at Tshwane University of Technology (where it carries out pilot-scale manufacturing of BMPs). As one of the few companies that has managed to take a product through all stages of development in South Africa, Altis recognized the shortage of good laboratory practice (GLP) quality animal facilities in South Africa and funded an upgrade of Tshwane's preclinical facility so that it would meet GLP standards. Its studies were then the first GLP-audited studies carried out at the facility, as required by ISO 10993 for medical devices. Nick Duneas, Altis's CEO, thinks that this model is a particularly good one for developing countries, providing a technology test bed in a lower-risk environment. "Because venture capital is so limited, you need to partner with academic institutions and willing private companies to develop your technologies into sellable products. The management of the relationship is critical though—you have to maintain focus and commercial vision while helping the institution to meet its objectives."

In terms of target markets, most interviewees did not consider a focus solely on the South African market viable because of the relatively small customer base. The few companies that did focus on South African and other African markets tended to have some kind of incentive to innovate in this area. Biovac's public–private partnership status, for example, has enabled it to invest in infrastructure and training in line with the Department of Health's priorities. Public procurement policies were highlighted as another powerful way to encourage companies to focus on local markets, but they were also seen as lacking transparency and failing to do enough to favor local manufacturers. In fact, some companies felt that high quality South African products were actually disfavored by procurement agencies, with preference going to well known European or North American brand names. For those companies interested in the African market, Carl Montague, health portfolio manager at the Lifelab BRIC, highlighted that "South Africa is a great point of entry from a US or European standpoint because you've got a structured system, and once you're here you can access the other markets. It's going to be a developing market as the prosperity of Africa increases . . . . I think there is a market here. People just don't expend much effort in investigating it."



South Africa's rich biodiversity is underpinning a range of activity in the private sector.

Most South African companies are focused on moving from local to global markets, although most of them are not yet generating a great deal of revenue from exports. Where possible, therefore, companies are investing up front in expensive quality control and regulatory approval (for example, GMP certification, WHO prequalification and CE marking) to meet global standards and establishing marketing and distribution partnerships with foreign companies. For some products—for example, such technologies as Disa Vascular's coronary stents—there is evidence that the local market can provide sufficient revenue to establish a company. Greg Starke, Disa's CEO, says, "The South African market is characterized by very high margins and a very big emphasis on new technology. Although the high prices result in tough marketing conditions, this market is a great place to build a solid revenue base." In the long term, however, issues such as lack of confidence in South African products and low production volumes pose problems, and many companies look to international markets for growth. At present, Disa earns 50% of its revenues from exports to countries in Europe, South America and Asia.

These approaches highlight considerable ingenuity in generating early revenue and minimizing costs. Even so, there is a limit to the amount that companies can do on their own, particularly when their aim is to become globally competitive. For several companies at an early stage of development which are funded by BRICs and pursuing R&D business models—a group that constitutes nearly half our sample—sustainability remains a challenge. As yet, most are generating minimal revenue, and the extra investments needed to develop products and technologies, which in the United States are made by venture capital funds, are not readily available in South Africa. Accessing international support is also extremely difficult, owing to low exposure of South African companies and to domestic regulatory constraints. In common with those in other emerging markets, South African companies are relying on trade secrets and forms of protection other than patents to protect their assets, as most do not have the resources to contest a breach of patent should that arise (**Table 5**). What's more, the relative obscurity of South Africa in the global biotech landscape means that foreign companies have often neglected to secure IP rights there; one South African-based company, Kapa Biosystems, has capitalized on this through its use directed evolution, a process covered by patents elsewhere.

On the other hand, unlike in other developing countries, South Africa's legal infrastructure for IP protection, which conforms to international standards, means that the mechanisms are there to protect inventions internationally should companies wish to do so. In terms of forming partnerships and raising international funding, a strong culture of IP protection should act strongly in South Africa's favor.

Barriers to development

Seven years since the publication of the South African government's National Biotechnology Strategy[7], some substantial barriers remain to the development of a dynamic biotech industry in South Africa. This section reviews the main challenges identified by domestic biotech SMEs operating in the South African environment.

Smart money is not smart enough. A major barrier highlighted by companies in this study is the lack of 'smart money' for biotech—private investors with an appetite for risk and an understanding of the nature of biotech investments. This issue has been raised for several years[9,13,14,18] and is still a major problem;

Table 5 Intellectual property portfolios and marketing rights for companies interviewed

Company	Patent information
ACRO	No patents
Altis Biologics	South African patent for process for purifying enriched mixture of BMPs from bone; co-owns a South African patent for a cross-linked collagen scaffold applicable to implants; patent filed for injectable bioassay system to test for osteoinductive biomaterials in rodents. Patents also pending in United States, European Union, Canada, Japan and China.
AngioDesign	Patent on crystal structure of the C-domain of the ACE molecule undergoing examination in Europe and the US; patent on crystal structure of N-domain of ACE molecule in national phase of Patent Cooperation Treaty examination; patents on new inhibitors where the three-dimensional structure of ACE was used for design and development also entering national phase
Arvir Technologies	IP owned by CSIR
Aspen Pharmacare	No patents; range of trademarks, copyrights and design rights
Bioclones	22 patents, including South African and Canadian patents on production by mammalian cell culture of mouse monoclonal antibodies; South African patent on EPO production from engineered baby hamster kidney cells and downstream processing by proprietary three-column process; South African, Canadian, New Zealand, Australian, UK, US, French, German, Swiss, Italian and Irish patents on retro-inverso synthetic peptide analogs; South African, European and Australian patent on process for the maturation of dendritic cells and production of dendritic cell vaccine
Biomox	International patent for an HIV immunosupportive supplement
Biovac Institute	No patents
Cape Kingdom	Patent on high-steam, low-vacuum process for oil extraction from South African herb buchu; trademarks registered internationally
Disa Vascular	No patents; focus on trade secrets
Elevation Biotech	No patents
Gknowmix	Exclusive license agreement for South African Medical Research Council for cardiovascular disease test, which is covered by a South African patent
Kapa Biosystems	No patents
National Bioproducts Institute	No patents
Synexa Life Sciences	Six patents in North America, Europe, and Australia for different processes and ways of using its Quorus Bioreactor technology, as well as other pipeline projects waiting to be patented
Veritrial	No patents
Vision Biotech	No patents

ACE, angiotensin-converting enzyme;

every company interviewed highlighted the lack of private finance as a source of frustration. The need for these funds is felt particularly at the stage before proof-of-concept, where there is a conspicuous absence of other funding mechanisms.

Many companies felt that South Africa has a strong pipeline of potential innovations that could have impact at home and abroad, but that lack of awareness of the healthcare industry by private investors is hampering these ever coming to market. In part, they attribute this to the absence of a high-profile South African 'success story' in the health biotech area to stimulate interest. One interviewee commented that "there's a lot of high-net-worth individuals who made angel investments in other sectors, but not in this sector because nobody's ever made it big in this sector in South Africa; there's no Mark Shuttleworth [a South African information technology entrepreneur] for biotech."

The impact of the small amount of venture funding that has been funneled into the area has been strong: "I don't think we could have started the company without it," says Paul O'Riordan of Synexa, "because the deals we were looking at from other capital providers were really not deals we could have done. They didn't understand the risks involved in biotech and tried to pass all of the risk to the entrepreneurs. Bioventures had a more knowledgeable and balanced approach. The important lesson here is that what we need is savvy venture capital, not just funding." Recently, Disa Vascular has raised European investment from Lacuna SICAV–Lacuna Apo BioTech (Basel, Switzerland; under advisory of Swiss-based Adamant Biomedical Investments, also of Basel)—a big step for a South African company. More venture capital funding could go a long way toward unblocking the South African development pipeline.

Sustainability of current business models. Strongly linked to the lack of venture capital financing is the issue of sustainability of a number of South Africa's R&D-focused companies, particularly those backed by government funds. Several are reaching critical points in their life cycles where they need to raise significant capital to support business development, and it is not clear where this support will come from domestically. This leaves companies with limited options—secure funding from overseas (for example, through acquisition by international organizations drawn to high-quality South African IP) or go public on an international stock exchange. Both of these scenarios entail the loss of South African IP from the country and, with it, most likely, vital human resources for the local biotech sector. The positive side of such transactions is that they enable technologies to reach the market and raise the profile and credibility of the SMEs that have nurtured them. Even so, accessing international funding is in itself no easy task, meaning that extinction is a real possibility. The European investment in Disa Vascular and the acquisition of Shimoda by a US company are the exceptions rather than the rule. A particular hindrance to such investments is exchange control regulation, which limits movement of capital and acts as a major disincentive for foreign investors.

Exchange control halts flow of innovation. As mentioned above, one of the most problematic pieces of legislation identified by SMEs was exchange control, in place to control all transactions involving flows of foreign exchange into and out of the country. Exchange control also applies to IP, thus limiting a company's ability to transfer patents offshore, affecting foreign investment and complicating potential exit strategies. As a result, South African biotech companies are more likely to sell out completely,

relocate or miss out on opportunities as investors opt for a friendlier environment elsewhere. Paul Abrahams, a serial biotech entrepreneur, cites an example of a South African colleague who relocated to the UK, taking his fledgling technology business with him, after frustrations with exchange control. "First of all, I think it's sad from a South African perspective because it's a fully South African–developed technology. But second, it's a lesson for the powers that be that people are actually resorting to that. They're actually going to leave the country and register patents elsewhere. I mean, if you've got intellectual property that's globally applicable, you should be able to transfer it where you want." Kapa Biosystems, founded by entrepreneurs from the United States and one of the few South Africa biotech companies that has received substantial overseas investment, also saw exchange control as one of the major downsides of operating in South Africa.

Given the barrier of inadequate local private financing, this regulation is doubly problematic. Although the government has said it is committed to phasing out exchange control, as yet, the necessary changes have not been felt by SMEs, and several interviewees were frustrated at the lack of awareness of the impact of this regulation at the SME level.

Skills and infrastructure gaps. Almost all companies identified lack of skills as a critical weakness for the growth of a South African health biotech industry. Recent research has shown that South Africa's human capital pipeline, particularly with respect to science and technology, is weak and is responding only slowly to the increasing demand for well qualified and competent scientists, engineers and technologists[19]. Although some interviewees commented on the weakness of tertiary education, the real issue identified concerned lack of industrial skills. The absence of a research-based pharmaceutical industry and the small size of the biotech sector mean that there are very limited apprenticeship opportunities for graduates, and as a result, many of them are employed in other sectors or look overseas for biotech and pharma experience. According to a National Biotechnology Survey carried out in 2003, ~50% of companies indicated that they had experienced shortages in human resources, listing a lack of skilled scientists at various levels, particularly MScs and PhDs, as well as quality-control staff, production engineers with pharmaceutical experience, bioinformaticists and protein chemists, among others[13]. A particular area of note is a lack of trained laboratory and production personnel with GMP and GLP experience; as South Africa looks to access global markets and grow contract services, this will be an increasingly important gap to fill.

The close connections between some companies and academia are proving to be significant in building up national skills and capacity. Synexa, for example, is located at the University of Stellenbosch's Medical School. Its bioprospecting program is carried out as a PhD project, with each PhD candidate being of previously disadvantaged background. CEO Paul O'Riordan points out that "we're going to help develop five or ten PhDs and MScs from previously disadvantaged backgrounds over the course of a couple of years. There is very little opportunity for people in South Africa to do this kind of research in an entrepreneurial setting, and combining postgraduate study with a career in biotech is an attractive option. It's a pretty big objective for everybody at Synexa and it's really the best contribution a small company like ours can make towards empowerment and transformation." In a similar vein, Grant Napier, CEO of Elevation Biotech based at Witwatersrand University, says. "There are a lot of synergies, with students with lead projects that are directed along the lines of our research. The most exciting thing in a way is the attraction of young people into science because it's a very exciting project that we're working on—antiretrovirals—and its opening a lot of projects that the university is benefiting from." In the clinical space, the African Clinical Research Organisation (ACRO) is responding to the shortage of clinical research associates (CRAs) to carry out clinical trials Africa-wide. ACRO aims to build capacity in the sector, including clinical trial site development, training of doctors and offering of CRA training courses in South Africa and other African nations.

In common with other countries, attracting and retaining the best talent from overseas to address critical needs will be increasingly important if South Africa's biotech industry is to develop as desired. For companies, slow turnaround times for work permits and other bureaucratic hurdles for foreigners were a frustration that undermined attempts to address their skills shortages. The idea of a 'green card' scheme—which proactively encourages workers in priority sectors and gives immigration authorities flexibility in permitting entry—has been suggested as a mechanism for South Africa to fill skills gaps[20]. Such a measure directed at biotech could well give the industry a needed boost.

A further factor with implications for human resources is the Broad-Based Black Economic Empowerment (BBBEE) program, developed, in response to the inequalities left by apartheid, to improve opportunities for previously disadvantaged groups. BBBEE includes such measures as employment equity, skills development, ownership, management, socioeconomic development and preferential procurement, and it sets targets for companies to reach. Although companies were very supportive of the BBBEE concept, they were aware of associated difficulties when running a small company. One interviewee said, "I do think it's a wise way, a comprehensive way, of tackling the thing meaningfully, but it's a heck of challenge because it's hard enough having to find qualified people. . . . I believe that the way out of this, though it will cost us a little bit extra, is to employ people with the relevant experience, qualifications, skills, etc., but in addition to that, employ 3 or 4 promising black people with the right credentials and have people nurture them and mentor them, so that in 3 or 4 years time when other projects come on board, we can then promote them into the project management of those projects." Indeed, several companies were creating opportunities for the next generation of black scientists and entrepreneurs and making significant contributions to skills development in the sector.

Improving students' exposure to the industry and its potential could make a big difference to the skills pipeline. One interviewee maintained that "probably the best way for the medical sector to grow up is if people coming out of institutions of learning believed that there were commercial things they could do. What do students do now? They either become sales reps, or they go overseas." Acorn Technologies' former 'Hellfire' program—which identified internships and other training opportunities for science graduates—was an attempt to increase industry exposure for younger scientists and was very successful but is no longer operational. At the time of writing, Cape Biotech was planning some human capacity development initiatives, which may include internship, business skill and specialist skills opportunities. Other initiatives include a careers website (http://www.biocareers.co.za/) that showcases opportunities in the biotech industry.

In terms of infrastructure, companies highlighted some key barriers to growth. Lack of preclinical facilities, particularly animal facilities, means that companies must contract out this work overseas, adding considerably to development costs. The CSIR is developing a plan for an international standard preclinical platform, which was due to be presented to the Department of Science and Technology and other departments in late 2008 and will, it is to be hoped, receive the necessary support. Interviewees also stressed a shortage of GMP contract-manufacturing companies and information technology limitations.

Box 6 Recommendations for biotech development in South Africa

On the basis of our study of South Africa's private health-biotech companies, we offer below eight recommendations to encourage continued development of the sector.

- Encourage private investment in the biotech industry— for example, through appropriate tax incentives.
- Expedite the removal of exchange control regulation for SMEs.
- Invest in improved preclinical research infrastructure based on the results of CSIR's survey of current and required capacity.
- Promote career development and recruitment in the following ways: facilitate the attraction of global talent to fill key skills shortages in the biotech sector (for example, through the use of a 'green card' scheme); support the development of local talent by SMEs (for example, through grants or through the BBBEE scorecard); develop more training opportunities for young people to gain industrial skills (either locally or overseas.); and offer entrepreneurship and business training to university students and SME staff.
- Improve turnaround times for clinical trial approval by regulatory agencies.
- Conduct an evaluation of the BRICs so as to consolidate best practice and develop realistic goals for the new Technology Innovation Agency, including suitable measures of success.
- Improve transparency and consistency of procurement processes to encourage local innovation.
- Continue to raise the profile of South African private sector activity internationally through attendance at trade shows and other networking opportunities.

Academic culture clash with the private sector. As in many emerging countries, the interface between academia and private sectors in South African is often problematic and generates several barriers to entrepreneurial activity. One of these is the 'academic mindset': it was generally felt that academics were still not encouraged toward entrepreneurship and valued publications more than patents. One interviewee, who had turned to commercial activities from a public-sector background, said that "South Africa's academic community has come from a very well-regimented political system where academicians researched and taught students. It was frowned upon to have an entrepreneurial streak in you." Most companies felt that it would take time for this to change.

Difficult and protracted IP negotiations were also a problem, with one interviewee commenting, "I would say that the South African IP policy of universities is more than 100 years old. It just does not favor entrepreneurship." The recently developed Intellectual Property Rights from Publicly Financed R&D Bill by the Department of Science and Technology is an attempt to address IP issues, harmonizing IP policies across organizations. Spurred on by the low number of patents originating from government-funded South African institutions, the new legislation takes its cue from the US Bayh-Doyle Act, in which universities and research institutions are granted ownership of inventions developed with government funds, in an attempt to promote technology transfer[21]. Some researchers have, however, raised concerns over the bill, as restrictions on licensing conditions may restrict marketability of IP. Tackling IP issues will also require building technology transfer capacity in universities. Again, this has improved over the past decade, but it is a fairly new phenomenon that is still finding its feet. Several challenges remain to developing this area, such as few invention disclosures, high costs associated with patenting and lack of experienced technology transfer practitioners[22].

These are important concerns, given that South Africa's innovation strategy has focused mainly on the commercialization of publicly generated IP. The emphasis—perhaps overemphasis—on the role of the public sector in innovation has been highlighted by other commentators[23], who consider it to have come at the expense of supporting the private sector, and private-sector R&D in particular. Recently, a review of innovation in South Africa by the Organisation for Economic Cooperation and Development (Paris) stated that "a major gap in current innovation policy is the lack of comprehensive support to innovation in SMEs"[20]. In this respect, the announcement in the 2006–2007 budget of a 150% tax deduction allowance for R&D expenditure in the private sector is an encouraging development.

Regulation failing to keep pace. A challenge that many companies raised was the capacity of the South African Medicines Control Council (MCC) to deal with the regulation of certain products and with clinical trial approval, particularly within realistic timeframes. For the most part, this was attributed to lack of capacity, resources and development within the MCC. In the clinical trial space, interviewees raised concerns that long timelines (sometimes as long as 18 months) for clinical trial approval were driving businesses away from South Africa, a particularly problematic trend, given the existing strength of the domestic service industry. According to one interviewee, "Over the past 10 years in the clinical trials business we've probably seen 30–40 trials move offshore, out of South Africa, on the basis of long timelines." However, at the time of writing, the MCC is addressing this issue and reviewing other regulatory systems worldwide for best practices. Christopher Whitfield of Batswadi Pharmaceuticals and cofounder of ACRO is hopeful: "There is likely to be also a big push once it's improved and hopefully within a year this stumbling block for growth is going to be eliminated. Much in the same way that in India they modified their regulatory systems to be more accommodating to phase 1, phase 2, phase 3 trials and post-approval, it's just a matter of time before the stops come out of the system."

Others raised concern about the capacity of the MCC to regulate new types of product outside the traditional pharmaceutical or generics areas (for example, biologicals, new chemical entities or complementary medicines). For some products—specifically, medical devices and diagnostics—minimal regulation means lower barriers to entry to these industries, but it is also a substantial barrier to establishing credibility. Greg Starke of Disa Vascular says ,"I think it's a negative thing now, very negative. Obviously it helped us in the beginning to develop implants . . . but it's a terrible thing if it gives [outsiders] an impression of bad quality. So in fact we went the EU route right from the beginning. We've had European approval since 2000 in fact, and we do everything in accordance with the European system now."

The regulation of alternative and complementary medicines also remains inadequate. Although draft regulations for the control of these products were produced in 2004, at the time of writing, these had yet to be implemented. Our earlier study also highlighted the absence of sufficient protection for biodiversity and traditional knowledge[9]. This came to light sharply in the case of *Hoodia gordonii*, a plant native to southern Africa with appetite-suppressing activity, long used by the indigenous San people to curb hunger on long hunting trips. The CSIR began research on *Hoodia* in 1963 and patented

its active ingredient in 1996, later licensing it to the UK company Phytopharm, which collaborated with Pfizer to investigate its synthesis as an appetite suppressant. Subsequently, the CSIR negotiated a benefit-sharing agreement with the San people, entitling them to a share of profits and any other spinoffs from the sale of *Hoodia*. Pfizer pulled out of the collaboration with Phytopharm in 2002, and so far, the *Hoodia* extract is still in clinical studies.

Stronger protection for indigenous biodiversity has come with the National Environmental Management: South African Biodiversity Act 2004 (ref. 24), which requires that prior informed consent be obtained and benefit sharing agreements made with stakeholders who provide access to indigenous biological resources and/or traditional knowledge for the purpose of bioprospecting. The specific regulations on bioprospecting, access and benefit-sharing set out in the act came into force on 1 April 2008. These specify the need for permits for any bioprospecting activity, other than that for basic research; for material transfer agreements for export of indigenous resources; and for benefit-sharing agreements that outline the manner in which the indigenous resource will be used and how the community will share in any benefits. The South African Patents Act has also been recently amended (Patents Amendment Act 2005) to link it to the biodiversity legislation, and it requires that all patent applications to the South Africa Patent Office must be accompanied by a statement on whether or not the claimed invention is based on an indigenous biological resource and/or traditional knowledge[25]. It remains to be seen whether these requirements can be implemented with minimal bureaucracy so as to stimulate rather than deter international cooperation in field of drug discovery from South African genetic resources.

On the basis of the barriers identified here, we make recommendations for the further development of the South African health biotech sector (**Box 6**).

Concluding remarks

Several years on from the publication of the National Biotechnology Strategy[7], South Africa's health biotech industry is showing tenacity in a challenging environment. Entrepreneurial activity continues despite significant barriers, not least the geographical isolation, which makes forming partnerships and reaching global markets difficult. Innovation is occurring in a range of diverse areas, capitalizing on South Africa's considerable strengths in R&D, biodiversity and medical infrastructure. Some areas of the industry are nominal—biogenerics are few and far between, and a fully South African developed drug is not on the horizon, given the current industrial and financial environment—but other R&D-intensive areas, such as medical devices, are showing strength, and interesting niche technologies with global appeal exist.

Even so, expectations for what could be achieved in a short time scale have perhaps been set unrealistically high. Compared with the sectors in other emerging markets, such as Brazil or India, South Africa's cadre of health biotech companies is small and very diverse. With several fledgling companies, the industry remains fragile and will need continued support if it is to flourish. Individual companies are small in size (all the SMEs interviewed were smaller than 150 people and about half had 10 employees or less) and modest in revenue (nearly 75% of companies interviewed earned less than $3 million per year, with several earning much less). The lack of critical mass in the sector is an issue in itself, resulting in few opportunities for local scientists, limited entrepreneurial expertise in biotech, and a lack of knowledge about the sector locally and internationally.

Government has provided a welcome kickstart to much of the biotech activity, with the BRICs and incubators at the forefront of biotech investment. Limited private sector funding, however, now threatens to compromise the long-term sustainability of newer, R&D-focused South African health biotech companies. Another clear message from the companies in this study is that a more holistic view of industry development is needed, with SMEs at the heart of the process. Although getting value from public sector research is critical, more emphasis needs to be placed on providing support to undercapitalized local companies that are struggling to compete on a global stage. Government should actively target the barriers facing SMEs. The negative impact of exchange control in securing outside investment, difficulties in obtaining work permits, slow regulatory approval times for clinical trials and procurement policies that seem in practice to be undermining South African products are all making it more difficult for health biotech SMEs to operate. Lack of key infrastructure, such as preclinical facilities and GMP contract manufacturing facilities, is also having an effect. South Africa cannot afford to lose ground here; for most companies, being globally competitive is the key to their sustainability.

Several companies in our study have proven that South Africa can generate interesting products for local and global markets, and that there are profits to be made—Disa Vascular's high-quality stents, Synexa's novel bioprocessing technology, Bioclones' human EPO and Vision Biotech's affordable diagnostics are diverse examples of South African innovation. Despite limited financing, their creative and resourceful business models illustrate a different way of doing biotech, which focuses on establishing a profitable business over a shorter timeline than has traditionally been found in many other countries. Such approaches should inspire confidence from investors looking to capitalize on South Africa's considerable R&D strengths. With a slightly different mindset, one that recognizes that small companies will need support and management to become winners, angels and venture capital investors could find a variety of investment opportunities in South African health biotech. And although local events—such as Bio2Biz, which brings together the South African biobusiness and academic communities—are useful in generating industry interest, South African health biotech's presence on the global stage needs continued support to improve opportunities for partnership and to build credibility.

In the areas of infectious and neglected disease, South Africa has had a few commercial successes (in vaccines, antibody production and diagnostics) and the recent addition of several new R&D-focused companies is an exciting development. Here the market extends farther than national borders, with companies developing distribution networks and supplying other parts of southern Africa. Thus far, these companies have relied heavily on BRIC funding; beyond this, there is little direct incentive for companies to invest in local health problems and there remains uncertainty about how these important endeavors will grow, given the substantial cost and capacity needed to move a drug along the development pipeline. One strategy for commercialization that has made some impact in South Africa is the product-development public–private partnership. For example, SAAVI (the South African Aids Vaccine Initiative) is making good progress with two locally developed HIV vaccines, which are nearing phase 1 clinical trials[26]. More recently, the nonprofit International AIDS Vaccine Initiative has awarded a grant to Elevation Biotech for the development and testing of new vaccine antigens that elicit broadly neutralizing antibodies to HIV. These are positive developments and should signal to global health foundations, among others, that there is capacity in South Africa to tackle vital health areas, with the right support.

Skills development remains a critical issue for South African health biotech. Young people need exposure to biotech industries and to be given opportunities to develop industrial skills. For those academics moving into

the commercial world, training in business and entrepreneurial skills would help, as would mentorship from those in the business community with experience in biotech. The contribution that SMEs are making to local skills development is considerable, and thought should be given to the best way of supporting this—through grants or shared costs, for example. Equally, attracting overseas talent to fill strategic gaps is a need for the future—streamlined processes to facilitate this will help. Getting commercial value out of the considerable strengths of the tertiary education sector will depend on ongoing capacity-building in business–research interactions, including IP negotiation and technology transfer expertise.

All of the stakeholders involved in the sector's development—from entrepreneurs to government funders, academics and private investors—have followed a steep learning curve and made substantial progress, considering the nascent stage of South African health biotech. Over time, the innovation system has evolved to become more workable and more adapted to the realities of the South African environment. This experience must inform future policy. As yet, there has not been a public review of the BRICs either to determine their progress or to measure the effectiveness of the BRIC model. This would clearly help, as part of the learning process and to set realistic goals for the future. The National Biotechnology Strategy is now under review, which is likely to yield useful data. At the time of writing, few details were known about the new Technology Innovation Agency, announced in the ten-year plan, which will coordinate all innovation activities. It is hoped that this agency will reduce overlap of different initiatives, set realistic measures of success and consolidate the considerable work done so far.

The South African health biotech sector has made considerable strides in a short timeframe. Nevertheless, it is unlikely to reach its full potential without more help. International partnerships and support will be needed to move the sector to the next level—be this accessing global markets, bringing in needed human resources or, critically, attracting outside investment. Lack of attention to any of these problems will slow the sector's growth or, worse, potentially result in a South African biotech sector that is stillborn. The examples in this article show that, given the right opportunities, South African companies can forge useful, long-lasting relationships with overseas partners, act as natural partners to global health foundations seeking to address developing world diseases, effectively access global markets and make strategic use of venture capital investment. What is needed now is the drive to make these examples the norm rather than the exception, easy rather than difficult. Only then can South Africa nurture its health biotech industry into adulthood.

Note: Supplementary information is available on the Nature Biotechnology website.

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The authors declare competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturebiotechnology/.

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