BIOMEDICAL SCIENCE

Can Money Turn Singapore Into a Biotech Juggernaut?

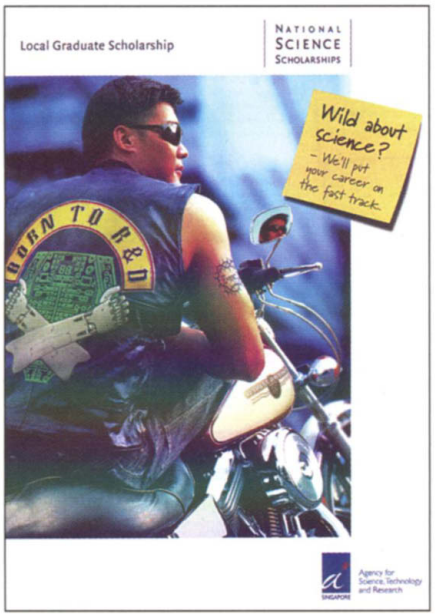
Singapore hopes a $2 billion initiative will create the talent pool and business climate needed for a world-class biomedical enterprise

SINGAPORE—Jullie Miller wasn't surprised when her husband, Lance, called from his office at the National Cancer Institute (NCI) in Bethesda, Maryland, one day in 2000 to say they needed to talk about a job offer he'd received. Miller had achieved some renown for using microarrays to capture genetic profiles of cancerous tissues, but after 3 years at NCI, the 30-year-old molecular biologist had begun to ponder the next step in his career. Because Lance had previously mentioned San Francisco as an attractive place to live, "my wife was thinking maybe the Bay Area or someplace else in California," Miller recalls. "When I said 'Singapore,' it blew her away."

It took the Millers nearly a year to make up their minds. They read books about the experiences of expatriates, sought the advice of friends and professional acquaintances, and weighed the likely impact on their two children, now ages 3 and 1, of a move to this tiny Asian city-state. Then they plunged ahead, he into the position of senior group leader for microarray and expression genomics at the fledgling Genome Institute of Singapore, she as trailing spouse and mother.

"We have a more active social life than we did in the States," Miller says about his new circle of friends, which includes transplants from Australia, the United Kingdom, and the United States as well as Singaporeans. He's equally enthusiastic about the job. "Building something from the ground up—where can you get that kind of opportunity?" he asks.

Singaporean officials hope that hundreds of scientists from around the world will join Miller in the next few years as the country seeks to make the products of biomedical research a pillar of its economy. Fueled by exports from the electronics industry, Singapore's 3.3 million residents trail only Japan and Hong Kong for the highest per capita income in Asia. But officials have long worried about the economy's narrow base. So in June 2000 Singapore announced its National Biomedical Science Strategy, which would pump an estimated $2 billion over the next 5 years into new institutes, academic research, and training in the life sciences, as well as tax incentives for both multinational pharmaceutical companies and homegrown biotech start-ups.



Rebel with a cause. A*STAR's Philip Yeo hopes that an unorthodox ad campaign will lure students into science careers.

It is an audacious bet on the direction of global science and technology. And it's no sure thing. Singapore needs to attract enough rank-and-file life science researchers to achieve a critical mass, and then it needs to keep them long enough to have an impact. A proportion of the Singaporeans sent overseas for education and training might well decide to stay abroad. And Singapore currently lacks the entrepreneurial environment that would nurture biotechnology start-ups.

But the gamble has already started to pay off. "Singapore has grown a biomedical industry within a very short period," says David Brantley, a technology policy analyst for the U.S. Commerce Department, who described Singapore's plans in a recent white paper (www.ta.doc.gov/reports/TechPolicy/Singapore_Biomedical_2002.htm). Direct foreign investment in the biomedical sector grew 6% last year, to $483 million. And the city-state is attracting some topflight scientific talent. Edison Liu, the head of the genome institute (who recruited Miller), also came from NCI, where he was director of the Division of Clinical Sciences. Recent arrivals also include molecular biologist Alan Colman and physicist Gunaretnam Rajagopal from the United Kingdom and cancer researcher Yoshiaki Ito from Japan (see sidebar on p. 1472). They are eager to help make their new country a biotech powerhouse. "Failure is not an option; it's a matter of the degree of success," says Rajagopal, who moved from the University of Cambridge last year to become director of the new Bioinformatics Institute.

CREDITS: A*STAR

The obvious answer

The idea for the biotech initiative came from the country's Economic Development Board (EDB). As the government's lead agency for managing economic growth, EDB has received much of the credit for helping develop Singapore's electronics industry in the 1980s. Exports are the lifeblood of Singapore's economy, and electronics account for a majority of those exports, fueling annual growth rates of 5% to 10% in the early 1990s. But the loss of electronics jobs to cheaper locations in Asia and the global downturn in the industry has triggered the worst recession in 30 years. At over 4%, unemployment is running near historic highs.

To reverse those trends, EDB decided to look for more knowledge-intensive sectors. Once that course was set, says Philip Yeo, co-chair of the board, the answer was obvious. "Nothing is more knowledge-based than biomedicine," says Yeo, who also leads the board's Agency for Science, Technology, and Research (A*STAR), which overseas public research institutes. "But we have to go beyond production. We need innovation capabilities, too."

Singapore already has a well-developed health care system that attracts wealthy patients from Malaysia and Indonesia. It has supported some clinical research, and a few individuals pursue basic research, including the high-profile efforts on human stem cell lines by reproductive biologist Ariff Bongso of the National University Hospital. Fortunately, a number of global pharmaceutical firms had already set up regional offices and manufacturing facilities in Singapore because of the assumption

that a rising standard of living among Asia's 3 billion people will lead to skyrocketing demands for better health care. The biomedical initiative, Yeo explains, is meant to combine these elements into "an integrated, goal-oriented approach to develop human, intellectual, and industrial capital" in the life sciences.

Biomedicine is only one part of the 5-year, $4 billion Science & Technology 2005 Plan, which includes efforts in information technology, materials science, and chemistry. But although A*STAR is vague about how much each sector will receive, life sciences are clearly a priority. A*STAR set up the Biomedical Research Council to focus just on life science research, leaving everything else to the Science and Engineering Research Council. The government also established a ministerial committee to oversee the biomedical initiative, as well as the star-studded International Advisory Council.

The advisory council isn't just window-dressing, says one member, Sydney Brenner of the Salk Institute for Biological Studies in La Jolla, California. He points out that the government heeded advice from him and others in the mid-1980s, when it was first considering a plunge into biotechnology. "We told them that before they had a biotechnology sector, they needed an overflow of scientists who had been working at the forefront of the field," he recalls.

The result was the Institute of Molecular and Cell Biology (IMCB), created in 1987 to train young scientists and conduct leading-edge research. IMCB's work, including the recent online publication of the sequence of the *Fugu rubripes* genome (*Science*, 23 August, p. 1301), has solidified Singapore's place on the global scientific map. "I used to go to conferences, and people were surprised that Singapore had any research at all," says IMCB researcher Graeme Guy. "Now everyone knows IMCB."

IMCB recently absorbed 12 research groups from the Institute of Molecular Agrobiology and might be renamed the Singapore Institute of Molecular Biology. Two new institutes, the Genome Institute of Singapore and the Bioinformatics Institute, will bridge the gap between basic and applied research. At the applied end of the continuum is the Bioprocessing Technology Centre, set up in 1990, and the new Institute of Bioengineering.

To encourage synergy, the institutes will be clustered in the new Biopolis, a $286 million seven-building development that will also have space for small companies. In addition to working in state-of-the-art labs, the researchers will share big-ticket equipment and animal-care facilities.

That cooperation extends to other government agencies, too. For example, the Ministry of Health is setting up the Singapore Tissue Network to accumulate a library of human tissues along with complete medical histories, as well as five national disease registries covering cardiology, oncology, myopia, stroke, and nephrology. Each will be governed by strict informed consent and privacy laws. In addition, the new Biomedical Research Council is offering grants to encourage life science research at Singapore's universities. There are also schemes to support clinical research.

Whereas Brenner says that putting everything "under one umbrella called biomedical research [is] what everybody who's got a decent medical research organization does these days," Colman worries that such an approach risks spreading the limited number of people and resources too thinly. Singapore must instead "concentrate its efforts," says Colman, who is chief scientific officer of ES Cell International, a Singapore company set up to commercialize the human stem cell research done at Singapore's National University Hospital.

LEADING BIOTECH INSTITUTES

INSTITUTE OF MOLECULAR AND CELL BIOLOGY
- Established in 1987, it has recently absorbed several groups from the Institute of Molecular Agrobiology (established in 1995).
- Search under way for director
- Total staff (combined): 490

BIOINFORMATICS INSTITUTE
- Opened July 2001
- Gunaretnam Rajagopal, director
- Projected staff: 100

BIOPROCESSING TECHNOLOGY CENTRE
- Opened 1990
- Miranda Yap, director
- Total staff: 100

INSTITUTE OF BIOENGINEERING
- In planning stage
- Director to be named
- Staffing levels undecided

GENOME INSTITUTE OF SINGAPORE
- Opened May 2000
- Edison Liu, director (right)
- Projected staff: 150

Changing minds

The lack of human capital might be an even bigger challenge. With few Singaporeans working in or even studying the life sciences, most of its research community is likely to be recruited from abroad. In fact, only two of 35 principal investigators at IMCB are native Singaporeans. At the same time, IMCB deputy director Hong Wanjin says that many of the principal researchers have been there for a decade or longer, and four have decided to become citizens. A*STAR hopes that investing in everything from grade school science fairs to scholarships for graduate students will eventually reduce the country's dependence on foreign scientists.

The Ministry of Education is also getting into the act by reforming the country's primary and secondary school science curriculums. Singapore's four polytechnics, which provide post-secondary vocational education, have all set up courses for biomedical lab technicians and research assistants. And the National University of Singapore has just revamped its life sciences curriculum and is putting a greater emphasis on research in response to the new grants program.

Singaporean officials hope all this effort will make biomedicine the fourth pillar of the economy—after electronics, chemicals, and precision engineering. After all, Yeo insists, the goals are jobs and products, not Nobel Prizes. "You only get, what, $1 million, and then it's split three ways," he says, ignoring the scientific bragging rights that come with the award.

Three companies have already taken advantage of the new special incentives to set up R&D operations in Singapore. Lilly Systems Biology, a subsidiary of U.S.-based Eli Lilly and Co., expects to have

CREDITS (TOP TO BOTTOM): IMCB; (TABLE SOURCE) A*STAR; GENOME INSTITUTE OF SINGAPORE

The Lure of First-Class Science

"Why Singapore?"

Hong Kong–born cancer researcher Edison Liu has heard that question a lot in the 18 months since he quit as director of the Division of Clinical Sciences of the U.S. National Cancer Institute (NCI) in Bethesda, Maryland, to head the new Genome Institute of Singapore (GIS). The tiny city-state is a long way from the scientific mainstream, its equatorial climate is no picnic, and its reputation as a buttoned-up society with draconian law enforcement turns off some researchers.

Liu cites the "consonance" between his goals and Singapore's interest in using genomics to address human health issues and the challenge of helping build up a rudimentary biomedical infrastructure. He also wanted to be part of an era, not seen for centuries, in which Asians are achieving at home the kind of peace and prosperity previously available only through emigration. "If I can assist that [trend] and at the same time have fun, that would be great," he says.

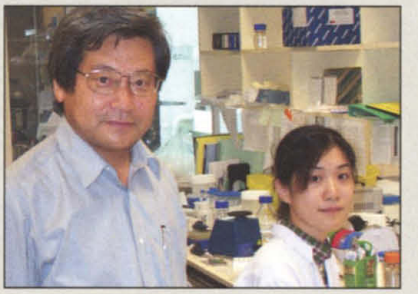
Singapore's biomedical strategy depends on finding more people like Liu. Two new institutes—GIS and the Bioinformatics Institute—are now recruiting a total of 250 researchers, most of whom will likely come from overseas. The Institute of Molecular and Cell Biology (IMCB), which recently absorbed 12 research groups from the Institute of Molecular Agrobiology, is looking for a director. The planned Institute of Bioengineering will require more foreign talent, and both universities and new industrial R&D facilities are turning to the international market.

Four who flew in. (*Clockwise from top left*) Lance Miller; Yoshiaki Ito and student; Alan Colman, and Gunaretnam Rajagopal all said "yes" to Singapore's research opportunities.

For scientists of Chinese and Indian ancestry, Singapore offers a chance to do first-class research in an environment that's familiar and, often, close to home and family. Gunaretnam Rajagopal, an Indian-Malaysian physicist who left the University of Cambridge, U.K., to take the top post at the Bioinformatics Institute, says he came "because I believe in their grand vision [for biomedicine]" and because it's just a short plane ride away from aging parents who still live in Malaysia.

Biochemist Barry Halliwell doesn't have personal ties to the region. But after spending a sabbatical from King's College London at the National University of Singapore in 1998, he returned in January 2000 to become chair of the biochemistry department. "I saw this was a place where a lot of things were going to happen and where I could make a contribution," says Halliwell. For molecular biologist Alan Colman, formerly of PPL Therapeutics—the U.K.-based biopharmaceutical company that produced Dolly, the cloned sheep—Singapore provides research opportunities that are no longer available at home. Colman is now chief scientific officer of ES Cell International, a company formed with Singaporean government support to commercialize the stem cell work pioneered at Singapore's National University Hospital.

Japanese cancer researcher Yoshiaki Ito responded to an offer to continue investigating the role of a gene called *RUNX3* in stomach cancer after reaching Kyoto University's mandatory retirement age of 63 this spring. Private Japanese universities offered him a slot, but IMCB agreed to employ all 10 of the 14 members of his team willing to move. It took them just 3 months to get the research back up to speed, he says.



Lance Miller, a microarray specialist who followed Liu from NCI to GIS, says that his family—his wife and two small children—adjusted quickly to the move. "I've become a salesman for Singapore," he says. The sizable number of expatriates and English as the official language helps, too.

Still, "Singapore isn't everyone's cup of tea," warns Colman. The government's low tolerance for criticism puts a damper on the arts, which he says means that "there's not much culture." And the long-ruling People's Action Party and a compliant judiciary combine to hamstring opposition political parties to an extent that seems excessive to many Westerners. "The Singaporean government does a lot of things differently," says Miller. "But it also makes possible this environment for science."

At the same time, most foreign researchers remain untouched by domestic politics, and many citizens and short-term residents say that the government in reality is far less heavy-handed than its reputation might suggest. "I don't think Singaporeans are walking around in constant fear of getting caned," says IMCB molecular biologist Uttam Surana with a chuckle.

If "Why Singapore?" is the first question departing recruits hear from friends and colleagues, the second most common query might be, "When are you coming back?" Most envision returning home at some point, although not soon, they say.

Workplace longevity isn't a problem for Liu, who says he doesn't even want people to stay until they retire. Instead, he believes that a natural flow of people is a way to keep an institute alive and to seed international collaborations. "This is not a dead end," he says. "But it could be a way station that will add value" to someone's career.

–D.N.

about 50 scientists working on computational tools for drug discovery by next year. Swiss pharmaceutical giant Novartis hopes by year's end to have the first of 60 researchers at work on treatments for drug-resistant tuberculosis and dengue fever at the new Institute for Tropical Diseases. And a trio of Japanese companies led by Chugai Pharmaceutical earlier this year jointly set up PharmaLogicals Research, with 10 researchers studying diseases prevalent in Asia.

Paul Herrling, head of pharma research for Novartis, says that Singapore's biomedical initiative enhanced its reputation for offering scientists a stimulating work environment. "Singapore has already attracted some big names," he says, so "it was quite a nice match."

The longest shot among Yeo's bets is the one placed on biotechnology start-up busi-

CREDITS: (LOWER LEFT) BIOINFORMATICS INSTITUTE; (OTHERS) D. NORMILE

nesses. As Singapore learned in electronics, a multinational company won't hesitate to move manufacturing jobs to a lower cost site. But a homegrown company would be likely to maintain a presence even if its factories are elsewhere. And start-ups create a wider variety of high-level jobs. "If a scientist quits [a research lab] and forms a company," Yeo says, that person "also hires a president, a general manager, a head of logistics." To encourage the transformation, researchers at A*STAR institutes can go on leave for up to 3 years to launch a business. EDB will even provide $150,000 in no-strings-attached seed money.

That model ignores several key factors in the start-up equation, says Alex Thian, a former patent attorney who now heads Research Biolabs, a small Singapore-based company offering biomedical research supplies and services. "You would have to raise more than $1 million to take a basic research idea through proof of effectiveness," he says, "and you'd need even more money to take it through clinical trials." He adds that Singapore lacks sources of early-stage venture capital, people who can evaluate start-up business plans, and managers with start-up business experience.

Then there are the cultural impediments to striking it rich. Gurinder Shahi, a molecular biologist and CEO of BioEnterprise Asia, which tries to help promising biotech businesses, says that Singaporeans prefer a stable job with a big corporation to the uncertainty of a start-up. Singaporeans are a bit uncomfortable with anyone getting too much more successful than their neighbors, he says: "There is an antihero mentality here." The electronics industry is a good example, he points out: Despite a large number of talented engineers and businesspeople and decades of experience, Singapore has produced just a handful of globally significant companies.

Shahi says that changing the culture, developing entrepreneurial-minded scientists, and creating a nurturing environment is a slow process. Yeo agrees, acknowledging that it will take until 2005 to get the new institutes up to speed and perhaps a decade for students to emerge from the pipeline. Miller says he's comfortable with that timeline. Although he anticipates someday returning to the States, in the meantime he expects to see a lot of good life science results coming out of Singapore: "That you can count on."

–DENNIS NORMILE

CREDIT: JTC CORP.

Synergy. The Biopolis science park will be home to Singapore's biomedical institutes.

Many Asian Nations Grab for Biomedical Brass Ring

SINGAPORE—Late last year, executives of Artus, a German company that offers polymerase chain reaction–based disease diagnostic services and kits, started looking for an Asian site to build a test lab and office. They weighed government incentives, the availability of trained staff, and living conditions for managers dispatched from home. "We considered Singapore but finally picked Malaysia," says Michael Tillmann, managing director of the Hamburg-based company. The incentive packages were similar, Tillmann says, but Malaysia's reputation for having a more stable workforce, combined with lower wages, gave it an edge—and Artus opened a facility there this month.

Throughout Asia, countries are vying for biotech companies such as Artus to beef up what's seen as an increasingly important economic sector. "Countries that don't try to develop their biotechnology sectors will be left behind both economically and scientifically," says Svasti Jisnuson, a biochemist at Thailand's Mahidol University in Bangkok.

In wooing foreign executives, countries tend to emphasize certain areas that set them apart. Singapore is emphasizing biomedical work, for example, leaving agriculture to China, which has more than a dozen genetically modified crops under production or in field-testing. Hong Kong hopes to identify and commercialize the active compounds in traditional Chinese medicines, and Malaysia is foraging through its tropical forests for agents that could be turned into food supplements and pharmaceuticals. Thailand is aggressively pursuing aquaculture, and Taiwan aims for a share of the global market in high-tech medical devices.

Some even see this variety as a strength. All of Asia could benefit from the synergy "as each country focuses on different but complementary biotech fields," says Gurinder Shahi, a molecular biologist and CEO of BioEnterprise Asia, an umbrella company for several biotech start-ups in Singapore.

But there are limits to diversity. Practically every Asian country has mapped out a strategy for biotechnology, Shahi says, "and in terms of establishing an infrastructure, they are all very similar." The plans typically include incentives for internal investment, increased governmental spending on life sciences, scholarships for students, schemes to transfer public lab discoveries to the private sector, support for start-up companies, and the creation of new institutes and science parks to house them. Even the names are similar. Singapore is building Biopolis to house its life science institutes. Malaysia plans to build three new life science institutes in BioValley. Korea's Seoul National University is planning BioMAX, a multidisciplinary biotech research institute.

Although the plans might appear to be offshoots of the same plan, potential recruits often see greener grass when they look beyond their own borders. Kim Sungyoung, a molecular biologist at Seoul National University whose work has given rise to one start-up company, envies Singapore's comprehensive planning. "We can't get that kind of cooperation among the different ministries in Korea," he says.

Shahi likewise envies South Korea, which already has more than 300 biotech businesses in operation, compared with only 30 in Singapore. Even if the number of start-ups in proportion to population is roughly equal, he says, the low absolute number in Singapore means there isn't enough business for major venture capital firms to maintain a presence or offer the kind of managerial advice available in South Korea. Getting a bunch of biotech start-ups up and running, he notes, doesn't generate the same headlines as signing up an internationally known researcher (see sidebar on p. 1472). But it could produce a bigger economic payoff in the long run.

–D.N.