Biopolis: Asian Science in the Global Circuitry

MICHAEL M.J. FISCHER

Biopolis is the major life sciences investment by Singapore to become a global player in a new knowledge economy, as well as a promissory construction*, a future-oriented emergent form of life constituted by and constitutive of a series of* ethical plateaus *or terrains of decision-making under entrepreneurial, policy and scientific conditions of risk and inadequate knowledge. Singapore's Biopolis partakes in general cultural shifts towards biological and ecological sensibilities as responses to fears of pandemics, climate change, destruction of biodiversity, and toxicities produced by industrial agriculture and manufacturing. The issue is learning about biorepair mechanisms and creating new ecologies of knowledge involving not only interest in infectious or chronic diseases but also stem and iPS cells, cancers and regenerative medicine. Using the Genome Institute of Singapore's first ten years as a partial focus, this article suggests metrics of success (beyond merely money, jobs, patents) which lie in three arenas: infectious diseases, cross-national science diplomacy and regenerative medicine. In October 2010, Biopolis underwent a sudden shift towards 'industrial alignment', raising ethical questions about the nature of future biologies, bioeconomies and bioecologies that have been spliced into the messenger RNA of different social networks and technical platforms of emergent twenty-first century biological sensibilities.*

Acknowledgements: This essay was written at the Asia Research Institute, National University of Singapore in January and July 2011, and revised in December 2011, as part of the work of the STS cluster, and I am deeply grateful for ARI's support, and especially of that of Greg Clancey, the leader of the STS Cluster, Lily Kong and Prasenjit Duara, the directors of ARI, and the members of the cluster and the participants in the January 2011 conference, 'Biopoleis'. I am indebted to Edison Liu, the Director of the Genome Institute of Singapore, and President of the Human Genome Organisation, for access, and many conversations over the years, as well as to PIs, graduate students and postdocs at GIS, including those named in this essay who have had an opportunity to respond to the draft of this essay: Bing Lim, Kyle Loh, Frank McKeon, Wa Xian, Martin Hiebberd, Lawrence Stanton, Ruan Yijun, Patrick Tan, Swaine Chen, Hervé Thoreau, J.J. Liu, Tom Lufkin, Alan Colman, David Lane, Neale Clark, Pauline Ng, Niranjan Naranjanan, Shyam Prabhakar, Paul Robson, Tara Huber, Ng Huck, Melissa Fullwood, Rob Kozma and Diane Hon. Beyond GIS, many have also contributed insights, including Philip Yeo and George Yeo; Chia Kee Seng and Sanjay Swarup at NUS; Huynh Hung and Soo Khee Chee at the National Cancer Institute; and members of the MIT-Singapore Alliance, especially Jianzhu Chen and Adam Drake.

Michael M.J. Fischer, Andrew W. Mellon Professor in Humanities, Professor of Anthropology and Science and Technology Studies, Massachussets Institute of Technology (MIT), USA.
E-mail: mfischer@mit.edu

Science, Technology & Society 18:3 (2013): 379–404
SAGE Publications Los Angeles/London/New Delhi/Singapore/Washington DC
DOI: 10.1177/0971721813498500

This essay charts three signature arenas of milestone successes and on-going challenges—in infectious diseases (SARS, dengue), cross-national science diplomacy (HUGO, SNPs Consortium), and regenerative medicine (cancer biology, stem cells)—of the Genome Institute of Singapore (GIS), in its first two five-year phases (2000–2010) as probes of progress and challenges for Singapore, the global health community and the global republic of science.

To *ethnographically* study an *emergent enterprise* such as Singapore's Biopolis (the bioscience research 'city' in which GIS is located)—or *ecologies of creative and innovative* new life sciences communities—requires finding appropriate modes of multi-locale access to *experimental and decision-making platforms at scales* ranging from that of individual scientists' trajectories (and rivalries), funding priorities and procedures, creation of multi-disciplinary projects or new fields with new instruments and methods, to long term strategic plans and pragmatics within national and global arenas of competition. Other preliminary accounts of Singapore's Biopolis have tended to operate at a macro-scale, describing the shifting political economies and their slogans (from Singapore as 'intelligent island' in the phase of investment in electronics and digital technologies, to the current phase of investment in the life sciences; as a mobilisation of Singapore's population as neoliberal capitalist work force and bio-available medical research subject, or as a distinctive neoliberal exception, racially defined as 'communities of fate' (Clancey, 2012; Koh, 2011; Ong, 2007, 2010, 2013; Waldby, 2009a, 2009b). The present essay attempts a more fine-grained, science-inflected, perspective on Singapore's effort to be a platform for innovation in the biomedical sciences.

A reset button was pushed on that platform in October 2010. It attempted to realign Biopolis towards industry and away from only basic science. After two five-year periods of multi-billion dollar investments, as the third five-year period began in April 2011, the long-talked-of hopes for returns on investment (financial, intellectual property, jobs, therapies) were foregrounded, and cooperation with clinicians and industry became a requirement for 30 per cent of Biopolis budgets.[1] Biopolis, after all, is under A*STAR (Agency for Science, Technology and Research), the Biomedical Research Council (BMRC), and the Economic Development Board (EDB), all under the Ministry of Trade and Industry, unlike the universities which are under the Ministry of Education, or the Campus for Research Excellence and Technological Enterprise (CREATE), which is under the Prime Minister's Office.

October 2010, however, was a sudden shock, with little or no warning to the scientists, though not the first one they had experienced. The same administrators in 2008, with similar suddenness, shut down the Singapore Cancer Syndicate. In June 2011, the same fate was dealt to the Singapore Biobank (previously the Singapore Tissue Network). The Singapore Consortium of Cohort Studies (SCCS) was also suddenly downsized, after a series of international 'reviews' until the correct one was returned by foreign reviewers. For some, it raises questions about management style and governance, while for others these decisions are part of an experimental ecology among multiple competing and potentially synergistic models of organisation. Singapore's universities are in a growth mode, shifting from teaching institutions

to becoming high-profile research universities. This is manifested by the building of a fourth flagship university (the Singapore University of Technology and Design, SUTD, in association with MIT and Zhejiang University); two new medical schools, one with Duke at NUS (graduating its first class in 2011) and one with Imperial College at NTU; and a new public health school at NUS. CREATE is a third organisational form—an alliance mechanism for collaboration on five-year renewable projects with foreign universities. Temasek Life Sciences Laboratories is a non-profit set up in 2002 by the government's Temasek Holding Company, in association with both NUS and NTU, and has a focus on plant and habitat life sciences. And there are also models such as the National Cancer Centre, that positions itself between the public health care system, SingHealth, pharmaceutical companies, NUS, and the Ministry of Health.

The stories of the aftershocks following the 2010 reset, two-year downsizing and recovery process, and the wider organisational experimental platform of Singapore, are topics for another time. But the story of GIS' signature arenas of milestone successes—in infectious diseases, scientific diplomacy, stem cell and cancer biology—are critical to establishing metrics of success that are not just monetary.

GIS gained world attention with its identification of five strains of the SARS coronavirus in 2003. GIS and HUGO, the Human Genome Organisation, under the leadership of Dr Edison Liu, pursued scientific diplomacy with the early Pan-Asian SNPs Project, now to be extended through a more disease-focused and denser array Phase 2 of the project. The most fundamental of the three milestone arenas of GIS successes has been the steady production of peer reviewed publications in stem cell, iPS (induced pluripotent stem) cell, microRNA, and cancer biology, as potentially revolutionary paths towards regenerative medicine, infectious disease control, cancer treatments, as well as basic science understandings of our molecular workings.

I begin with the SARS story, which provides: (a) one of the first examples of genomic tools deployed to contain a pandemic; (b) a call for better disease or biosecurity global reporting and responsiveness; (c) one of the first effective uses of the Internet to foster a change in World Health Organisation (WHO) reporting; (d) a case-study in competitive-cooperation among international labs (and competition in retrospective historical accounts for significance); (e) an exemplar of coordinated response within urban governance; (f) and, in the aftermath, a case study in modular response to subsequent pandemics (Mexico and the H1N1 'swine' flu of 2009) and a demonstration that the concerns of benefit sharing remain unsolved (Indonesia and the H5N1 avian flu of 1996–1997).

Genomics and Infectious Disease: SARS and Global Biosecurity

sosick.org (SARS website, Hong Kong)

The 2002–2003 effort to identify and design a diagnostic kit for the lethal, fast-spreading, and initially mysterious severe acute respiratory syndrome (SARS)

provides one of the first examples of genomic tools deployed rapidly and effectively to stop and contain a pandemic. It was a scary time. Stem cell biologist Bing Lim recalls:

> For one year, we stopped most of what we were doing and everybody pitched in to help where they were needed. . .Most of it came from the sequencing group. For us in the stem cell group, our focus was more on the biology, the biology of infection, lung damage...the process of ARDS (acute respiratory distress syndrome) whereby a large part of the damage is secondary to an inflammatory response. The thing that kills at the end is a lot of inflammation, hemorrhage, embolism, clotting, the lung becomes literally a soggy mass which cannot exchange oxygen. (28/6/2010)

It also was a global wake up call for global reporting of infectious disease outbreaks. Old-style government health politics of not reporting epidemics, out of concern for national pride or the desire not to admit inability to provide protection, are no longer feasible. In the past, many countries suppressed information about cholera or other seasonal epidemics. In 2002, the Chinese government was slow to report outbreaks of SARS that began in the Guangdong province, and then spread to Hong Kong, Hanoi, Singapore and Toronto. This incident is said to be the first time high-level Chinese officials lost their jobs over an epidemic: Health Minister Zhang Wen Keng was replaced by Wu Yi, and China joined the global effort to contain the epidemic. Public health infrastructure and emergency protocols thereafter became a Chinese priority.[2]

The SARS crisis also provided a celebrated example of one of the first effective uses of the Internet to get information out to the world. WHO was slow in forcing China to reveal the problem because WHO policy until then was to accept only reporting of disease outbreaks from national governments. The crisis changed that policy. Trust and cooperation are key to providing a globally distributed network of facilities with regional centres that can be quickly mobilised for epidemic and pandemic emergencies. Social media, the Internet, and cell phones provided cover for more censor-vulnerable Chinese newspapers to report the story after it appeared on the Internet, and are, thus, forcing old reporting systems to become more nimble.

The response to SARS also provides lessons of multi-disciplinary and multi-institutional cooperation, as well as *competitive* global coordination. The competition to be the first to sequence and genetically identify the virus was closely contested by labs in Vancouver (identified the first strain), Atlanta (identified the Hanoi strain), Singapore (identified five strains) and Hong Kong (two strains).[3]

Although much was made of SARS as a call to establish more robust global-monitoring collaborations and systems, subsequent experiences with avian and swine flu pandemic scares renewed calls to improve global public health infrastructures, build trust among national health ministries, and devise new bottom-up social infrastructures that actively involve frontline physicians, health care workers, and scientists. Indonesia declined to share samples of its avian flu strains with Singapore

and the international community on the defensible grounds that while it is expected to provide samples to the world, vaccines and drugs developed are rarely made available to its population (Khor, 2007). As it turned out, the culling of backyard chickens, that was insisted upon by international agencies, may have been misdirected, and was resented, since the virus most probably came from large industrial chicken farming (Lowe, 2010; Sparke and Anguelov, 2011). The involvement of international organisations and of the US military health support laboratories in Indonesia in insisting on this policy of culling did not bolster public confidence or trust.

The SARS coronavirus, together with the 1996–1997 fast-mutating, highly pathogenic H5N1 avian flu, and the 2009 H1N1 swine flu (first thought to be a re-assortment of four human, avian, and swine strains, but later found to combine only two swine-originating strains),[4] are only some of the half dozen or more efforts in which genomics and the social infrastructures necessary for genomics deployment have become basic tools. Efforts to contain multi-drug resistant tuberculosis, to find new drug combinations and vaccines for malaria and HIV/AIDS, and to design diagnostic kits for infections such as paediatric pulmonary diseases or Lassa haemorrhagic fever are among such efforts that contribute to a new techno-social terrain of infectious-disease management. Without genomics tools, efforts by public health services are reduced to hit-and-miss assumptions about what infectious strains exist in local populations and what drugs, therapies, or containments are most cost effective.

These tools need not always be the most expensive or complete suites. During the 2009 HIN1 swine flu outbreak, Mexico initially considered buying sequencing machines so as not to have to rely on the US's Centre for Disease Control, but through connections established via the HUGO network, Singapore's Genome Institute offered a simpler set of tools (Affymetrix arrays) with a support team. The H1N1 swine flu scare made clear the need to make more robust the earlier WHO designation of influenza centres around the world. WHO provides no funding, but merely recognises centres that have requisite capacities. Such centres need to be made interactive and cooperative in a global network as during the SARS crisis,[5] and as databases, research publications—and even to some extent research itself become more open source and public—these social infrastructures need to follow suit.

Indeed, civil society in both China and Hong Kong provided interesting harbingers. Two local civil society warning systems proved more effective than official ones. The SARS outbreak in Guangdong was first picked up from local Chinese reports via an electronic monitoring system on 27 November 2002 by Canada's Global Public Health Intelligence Network, part of WHO's Global Outbreak and Alert Response Network. But China did not officially report the outbreak to WHO until February 2003. As late as April 2003, Beijing was accused of undercounting cases in Beijing military hospitals.[6] Second, in Hong Kong, the first infection came with a physician from China who stayed on the ninth floor of the Hotel Metropole and infected others there and then in the Amoy Gardens Housing Estate. Concerned citizens created a website called *sosick.org*, which eventually forced the Hong Kong government to provide information in a more timely manner.

In Singapore, the SARS pandemic proved, thanks to an evolving containment strategy, to be largely a nosocomial infection. Of the first 13 cases, seven were health care workers; and of the total 238 probable cases, 155 (78 per cent) acquired the infection in hospitals, including eighty-four health care workers (C.C. Tan, 2005). Super-spreading events (one patient infecting ten or more others) can rapidly expand an outbreak: Singapore had five of these, Hong Kong had three. Yet, 299 died in Hong Kong, and only thirty-three in Singapore. In Toronto, of 251 probable cases, forty-four died.[7] The learning in 2003 allowed for a more modulated response in the 2009 H1N1 pandemic. At a transition point and due to the relative mildness of the virus, Singapore was able to move from containment to mitigation protocols, with input from the US. Centre for Disease Control and Prevention, but ahead of, and de-linked from, WHO alert levels. There were eighteen deaths in Singapore, but the country managed to simultaneously host the 2009 Asian Youth Games. As a Singapore Ministry of Health review notes (Tay, Ng, Cutter and James, 2010):

> ...monitoring diverse sources of information from around the world is resource intensive; fortunately, Singapore was plugged into an *informal* global network of public health professionals and organisations [which was] valuable in keeping the Ministry of Health abreast of a rapidly changing world situation. (p. 320; emphasis added)

In 2003, Prime Minister Goh Chok Tong attempted to take the lead in forging coordination of cross-border protocols at an ASEAN summit in Bangkok, including also China, Japan, and South Korea, but as the stories in this paper reveal, such efforts are still fraught.

The SARS story has two, double-helix like, threads: biotechnology and social infrastructure.

The Biotechnology Thread

From November 2002 to July 2003, a mysterious severe acute respiratory syndrome set off a worldwide alarm. The mortality rate was 9.6 per cent (774 deaths) of 8,096 known infected cases across 37 countries, according to the World Health Organisation (WHO). No efforts before this time had been put into antiviral drugs for coronaviruses, so no effective agents were initially available. At first, it was not even clear that SARS was caused by a coronavirus. The first indications came from pictures under electron microscopy from Malik Peiris' lab at the University of Hong Kong, showing spiky protuberances characteristic of coronaviruses. Further microscopy was conducted in Vancouver, Germany and the Pasteur Institute in Paris. PCR (polymerase chain reaction) amplification and comparison with genetic libraries indicated it was not a known coronavirus. Experiments infecting macaques at Rotterdam's Erasmus University fulfilled Koch's postulates establishing it as the causative agent.[8] To establish its genetic structure, in order to design diagnostics kits and therapies, required growing enough SARS virus particles to understand its biology, and its modes of mutation.[9]

The first samples in Singapore came from the pathologists at Singapore General Hospital, who took them from the first two patients to die. Ten Tock Seng Hospital was soon after designated the sole hospital for treatment and isolation of confirmed or possible SARS cases. SARS—like AIDS—is an RNA virus (one of the largest), and the initial fear was that, like AIDS, it might be so mutagenic as to be hard to stabilise long enough to establish targets to inhibit it. RNA viruses, having only one, rather than two strands of nucleic acid, are less stable than double-stranded DNA viruses, where one copy stabilises mistakes made during replication. Fortunately, SARS was not as quickly changing as AIDS. It did not, however, infect any of the human cell lines commonly used to grow viruses in the lab, and so the GIS virology team, headed by Dr Ling Ai Ee, switched to Vero cells (from the African green monkey); there, SARS was able to multiply. Next, in the effort to sequence the virus, PCR amplification was tried, but did not work. PCR amplification requires matching known genetic sequences with your unknown samples to produce primers, but the two coronaviruses whose sequences had been decoded did not produce any matches. So, Ling's team moved on to shot-gun sequencing, breaking up the SARS RNA into fragments and growing them in bacteria. On 12 April 2003, the Canadian Genomic Sciences Centre in Vancouver published the first sequence of a SARS strain, followed the next day by the Centre for Disease Control in Atlanta publishing the sequence of a strain from Hanoi.

The Genome Institute of Singapore sequencing team, led by Ruan Yijuan, followed on 19 April with five strains. Hong Kong followed with two more. All five of the Singapore strains carried a signature sequence of TTGTT, which allowed matching against known contacts, and led back to the Hotel Metropole in Hong Kong. Different strains all have similarly distinctive signatures. Computational analysis established that the mutation rate was only about 0.03 per cent per generation. So while it mutated, large chunks remained stable.

At this point, the GIS team led by Martin Hibberd, and postdoc Lisa Ng could begin designing diagnostic tests. Ng's PhD work had been on animal coronaviruses, so she could help identify which portions of the SARS genetic code to run through PCR tests to pick out those strands that might match known coronavirus sequences. But this still required running thousands of sequences through the PCR machines and waiting for results, and it required a supply chain of samples from patients. Initially, the samples were requested from nasal swabs, which required close contact between patients and nurses, which hospital administrators were reluctant to allow lest the health care staff become infected. There were frustrating delays in getting samples. Eventually, the high-level Singapore SARS Clinical Consortium worked out consent procedures and divided the workload among participating laboratories so that processing could be expedited. Samples were all routed through the Singapore General Hospital for distribution to the researchers. Eventually, Ng showed that the team's diagnostic tests worked on blood samples, so the need for nasal swabs was removed. The live samples all went to the BL3 lab (biosafety containment lab level 3) at the Defence Science Organisation, which extracted the RNA and passed it on to GIS, which turned it into double-stranded

DNA on which diagnostic tests could be run. The Institute for Microelectronics helped modify one of its DNA-extraction chips to extract RNA, and the Institute for Cellular and Molecular Biology helped identify markers to detect SARS antibodies and designed primers. Within a week, the Ng-Ruan-Hibberd team had developed a prototype diagnostic test, and asked other labs to test it. It performed extremely well—better than tests coming now from Hong Kong, Atlanta (CDC) and Germany. But it took much too long; and while it was very sensitive, it also was prone to contamination. So the next step was to get the process down to an hour. Once this was working, Roche licensed the technology and began mass producing the user-friendly diagnostic kits now widely in use.

Diagnostics are important but they don't solve all questions for developing therapies, such as how the virus works in the body, why some people are super spreaders of the virus, and why the virus affects some people differently. Since the events described above, various lines of research on therapies, including vaccines, have been initiated, and sequencing the genome has provided potential targets. One would also like to know the relations among other species that are subject to the virus. Ecological interactions are becoming a field increasingly open to molecular-level investigation.

The Social Infrastructure Thread

From the above biology and technology thread, it is clear that many actors had to work together. The sequencing technologies of genomics—along with older culturing, RNA extraction, PCR, and micro-array technologies—provided the precision not available in the age before genomics. The two-year-old Genome Institute of Singapore was a key player both in the local and worldwide efforts to contain the epidemic.

What is particularly remarkable about the Singapore story is the degree to which so many parts of the society eventually worked together under what could have been real chaos and a terrifying pandemic of the sort one reads about in historical accounts. On the ten-year anniversary of SARS, Wong Kan Seng, the deputy prime minister who led the inter-ministerial task force in 2003, reflected on the time of initial chaos, warned against complacency today, and focused on the non-medical, social infrastructure (W. Tan, 2013). In the beginning, health care workers were shunned, people moved away from nurses wearing uniforms on public transport, and taxi drivers refused to pick up or drop off anyone at hospitals. But nurses—especially foreign ones—and other hospital personnel heroically refused family calls to return home, insisting on their duty in a health care emergency. Five health care workers died from the infection. Managing food supply and arranging alternative housing for the quarantined in case of outbreaks in housing blocks were worries, and especially the need to allay the public fear that there might not be enough food, and thus prevent panic buying. Introducing video devices on home computers for the quarantined, instead of phone checks, made home-based monitoring easier. But Wong notes that in hindsight, the authorities should have isolated the virus at

Tan Tock Seng Hospital (TTSH) earlier than it did (22 March 2003). 'Before we stopped all visitors [coming] to wards, in many cases it was very hard work tracing those who might have come in contact with SARS patients', he notes, and indeed others remember there was chaos initially with hospitals refusing to share records and samples, because everything was decentralised. One of the first people with SARS was a diabetes patient with respiratory problems, who was turned away from Tan Tock Seng Hospital because 'we are a SARS hospital' and he had pre-existing ordinary respiratory problems. So he went to Singapore General Hospital where he infected others.

These details are critical in going beyond assumptions that the orderliness of Singapore made dealing with an unknown and complex crisis simple. Indeed, the fear was transnational, as in the case of a Singapore infectious-disease physician who felt ill on a flight via Germany and informed the crew. He eventually proved not to be infected with the virus. People in the health care and educational systems checked into hotels rather than take the risk of infecting their wives and children. Something of the feelings of urgency and willingness to risk one's own person is recounted in first-person memoirs and in the tracing out of all the jobs that had to be done, including off-duty nurses who rushed in to help and prison inmates in the Score laundry unit who washed the linens from the hospitals.

The ability to work across bureaucratic boundaries was facilitated at the highest levels. Not everything worked smoothly, as in the delay in getting samples mentioned above, or the failure to isolate some cases early enough. Later, there was a case of a misplaced infected vial that caused an illness (as also happened in Taiwan and China). But the sense of emergency and solidarity of a small city–state and nation proved effective (for contrasts with Hong Kong, where 299 people died as opposed to thirty-three in Singapore, see B.H. Chua, 2006; Leung et al., 2004; for the chronology of events, the best account is C.C. Tan, 2005; Tay et al., 2010 provides a particularly clear account of the shift from *containment* efforts as a way to slow the spread as a 'slow burn' rather than a 'wildfire', and the shift to a *mitigation* phase once the daily number of epidemiologically unlinked, newly diagnosed, and locally acquired H1N1 cases began to exceed the number of cases linked to contact with prior ones).

Even the idea of fever scanners was moved from concept to testing to implementation within nine days, relieving the manual stationing of nurses at the airport. The idea came from an American Nokia employee who had seen thermal imaging cameras in a Nokia plant in San Diego, and e-mailed the idea on 2 April to Health Minister Lim Hng Kiang, who then instructed the Defence Science and Technology Agency to investigate the idea. They, in turn, worked with the Singapore Technologies Electronics and Engineering company to modify existing infrared military technology (designed to pick up body heat) so that it would measure skin temperature as a proxy for core body temperature. This was tested at a hospital emergency room and the first modified units were installed at Changi Airport on 11 April. Scanners were then loaned to Hong Kong, Beijing and Toronto.

The speed of international competition and collaboration around the epidemic was, with exceptions, impressive. But at this level, things were (and are) not always as smooth as they might be. Indonesia's refusal to give its Avian flu (H5N1) sample to international scientists on the principled grounds that when Indonesia gives samples and vaccines are developed, they are not made available at an affordable price in Indonesia, is an important reminder that the construction of biosecurity systems is not seamless, and that there are paradoxical issues, matters of cultural arbitrage, and cosmo-politics. Not only are there issues of equity and access to care, but as a number of analysts have pointed out, causal mechanisms in the jumping of the species barrier and epidemic or pandemic generation are also not straightforward. It is quite likely that the Indonesia H5N1 outbreak as well as those in China and Southeast Asia were the result of industrial poultry production, and that efforts to blame backyard poultry production are misplaced. As anthropologist Celia Lowe (2010) recently elaborated, the resistance to international policing of the pandemic was supported generally by Indonesians at many levels of society, feeling that the massive international interventions constituted an unnecessary and counterproductive violation of national sovereignty.

In sum, genomics technologies are proving to be a force for change for infectious-disease identification, targeting appropriate drugs, tracking epidemiological patterns, public health monitoring and conducting basic research on pathogens and vaccines.

Genomics and Scientific Diplomacy

> The Japanese were saying, give me your DNA, and I'll work it out for you. The Chinese were stone-faced, knowing that sooner or later they will be able to do it all themselves and do a lot better than the Japanese. The Koreans would nod their heads, you know, gently, but afterwards sabotage anything the Japanese would want to do. And the Taiwanese and Chinese wouldn't talk to each other.
>
> (Edison Liu, joking about the social skills needed to work across national competitions; EL, 1/9/2009)

Three modes of building trust and collaboration across worlds of national agendas, scientific competitions and concerns over benefit sharing are—consortia, networks, and disease-specific projects. Each requires recursively building appropriate ethical procedures, building social infrastructure and leveraging already existing resources.

A. Consortia: Pan-Asian SNPs and Modelling Ethical Collaboration

To help generate collaborative research in the ASEAN region, the Human Genome Organisation, established a Pan-Asian SNP Consortium, inviting scientists in all Southeast and East Asian countries to participate in the collecting and analysis of samples, and drawing upon previous friendship networks to get started. Scientists

from resource- and biotechnology-poor countries would maintain physical custody of their samples, but be invited to work on the machines in more resourced countries. To make this work, it was decided to work on a migration study to help build up trust and working relations among scientists. Everyone, it was said, is interested in 'origins', and this might avoid countries feeling stigmatised if they were found to have a particularly high incidence of some disease.[10]

The initial Pan-Asian SNPs project was relatively small scale, and was intended to start building a *network of* people who trust one another based on past collaborations, as well as a *model for* protecting national sovereignty and scientific credit by ensuring that local scientists maintain chain of custody over samples, but are enabled to use, think with, and contribute to state-of-the-art technology and research platforms. It also explored models of ethical engagement with indigenous and minority communities to avoid the sorts of problems that derailed the Human Genetic Diversity Project (Reardon, 2005). In India, for example, labs were opened to children to see what was going on, as part of longer-term engagements, not single collecting events.

Phase 1 was like a low-resolution map. Phase 2 will expand the sampling and density of arrays, but as Edison Liu puts it, it will go beyond population migration studies, to begin to build multiple kinds of Asian reference sets. (EL3/2010)

Global collaborators—from George Church of Harvard to China's BGI—are mutually recruiting one another to enable the project to pioneer new whole-genome technological platforms, and sample in the thousands for stronger scientific breadth and depth than the original pilot SNPs project. Edison Liu says:

> A lot of genome studies are array based studies, based on patient information and genome sequencing from the Caucasian populations. That is the basis of Illumina's array design [used in the Phase I study]. It is still useful, it is still helpful for the Asian study, but it is definitely not optimal. We believe it is time for us to develop an Asian array, but in order to do that you need to have Asian sequencing information. We are trying to do that. We also want to see if we can build something more pharmaceutical, a very detailed analysis of all the drug metabolising enzymes. Pharma really wants to know how these different compounds are going to be metabolised in Asian populations. They want to know whether [different populations] have different dosaging [levels]. So we also try to build that component into that project, trying to see if we can build a little more detail on all the genes involved in the metabolism of drugs. (EL 3/2010)

At the March 2010 HUGO meeting in Dubai on Genomics and Heritable Diseases, informal meetings were held to help brainstorm the design, publicise the effort, and get new collaborators interested. Liu continued:

> There are a lot of difficulties, the samples, funding, how the samples are handled because a lot of countries do not have the technology to do their own study, at the same time they have issues to send the samples out of the country. The good

> thing from Phase 1 is that many of these issues already have a model to follow... It is a *network of* people, but it is *also a model*. Basically if you cannot do [the analysis] yourself, and you don't want to send sample out, why not send *your people* carrying *your samples* here and [after the analysis] carry your sample away. The sample never leaves you. (EL3/2010)

Some analyses can be done locally in many countries, others require more technology-enabled centres. With the introduction of third-generation sequencers (smaller, faster, fewer reagents), and genomics centres outside the industrialised world, the map of capacities will shift. The ability of GIS and the HGM to provide Mexico with alternative tools during the swine-flu pandemic of 2009, as related above, is already one such network effect.

In sum, while the Pan-Asian SNPs consortium—coordinated from GIS in Singapore—intended to contribute to scientific issues in migration studies, and to provide a testing platform for technology tools, it was arguably and more importantly dedicated to creating 'a *network of* people...*also a model*' for more open and participatory relations across national boundaries, and between minority and majority populations. It was intended to help build infrastructure, both of a bilateral kind, and of global pandemic warning and response systems for better decentralised, flexible and coordinated public health. The ideas build upon and leverage resources already in place such as the influenza centres, the BL4 labs, and the screening and coordination put in place in response to the SARS, avian and swine flu scares.

B. Networks: Clinicians, Research, Pharma

Huynh Hung at Singapore's National Cancer Centre, next to the Singapore General Hospital, provides a model of placing physician-scientists and clinician-research collaborations in a strategic nexus such that one becomes a centre of calculation and obligatory point of passage (Latour, 1988). Aside from organising a lab to work with SCID (severe combined immuno-deficient) mice that Huynh's lab has inbred for twelve years to make them as identical as possible (with minimal immune systems so that they accept human tumour cells more easily), Nuynh also works to ensure close relations with surgeons from whom he gets tissue, with oncologists whom he coaches to be interested in trying new drug combinations, and with pharmaceutical companies who provide new drugs that have gone through animal trials but need pre-clinical testing. In each case, he must figure out how he can help these collaborators. Since single drugs are unlikely to work—'Tumors are not stupid. If you use one drug against them, they will produce another protein which helps them survive.'[11]—any given pharma company is less well placed than Hyunh to test out combinations of drugs that may come from different companies. He is on call whenever surgeons in the operating theatre have a sample of interest, since these must be transplanted within ten minutes or so into an animal for it to be of use to the patient (to test drugs and dosages). With the closure of the Singapore biobank, he banks his own research tissues for the time being in his own lab and at NCC under the SingHealth biobank.

Hyunh is in position to track many moving pieces.[12] For Vietnamese patients, he can act as a translator to get them the care they need, but also track what drugs and treatments they undergo with what results. Hyunh himself was one of the boat people rescued in the aftermath of the American withdrawal from Vietnam, who made his way to Quebec, and eventually through French and English medium schools to Singapore. This is a fascinating cultural nexus—his own career trajectory as a thread in recent global history, and his ability to help Vietnamese patients while involving them as research subjects. This ability to tap cultural resources, as well as in his resourceful cultivating of collaborations in the hospital across communities of specialisation, has recently paid off with early successes in combining Avastin, the anti-angiogenesis drug pioneered in Judah Folkman's lab at Children's Hospital in Boston, and rapamycin, the mTor (mammalian target of rapamycin) pathway inhibitor that is used in immuno-suppression. In eighteen human patients, liver cancers have disappeared (1), decreased (2), or remained stable (7) in over half, extending survival rates from six to seventeen months.

Liver cancer is one of the cancers of interest to the government because of its prevalence in local populations. This is a hard-won case of translational medicine, which he and the National Cancer Centre hope the government will recognise as the sort of industrial 're-alignment' and practical returns that can also lead to other returns.

C. Disease-specific Projects: Ecological Niches and Transnational Collaboration

Singapore-born Patrick Tan splits his time between GIS—where he runs a genomics programme focused on tropical infectious diseases—the Duke-NUS Medical School, the Cancer Science Institute and the National Cancer Centre, where he applies genomics to cancers endemic in Southeast Asia. He also sits on the Singapore Bioethics Committee. His research has forged collaborations in Thailand on meliodosis and on a river fluke that can cause a lethal liver cancer, as well as on larger-scale collaboration with Japan and Australia on gastric cancer, developing a molecular library that hopefully can distinguish useful from non useful drugs indicated by patients' genetic profiles.

When meliodosis, caused by the soil bacterium Burkholderia pseudomallei, infects humans, the mortality rate runs around 40 per cent even in Singapore, where good ICU (intensive care unit) facilities are available. The US Centre for Disease Control, therefore, designates it a bioterror threat, and that fact negatively affects accessibility and funding. Researchers are supplied with strains that must be worked with in containment facilities. The designation makes it harder to exchange strains among countries. The paradox is that one could walk outside in many tropical countries, including Singapore, and isolate the pathogen from random soil samples. Before 2001, even in 2005, one could work with the pathogen simply on the bench. Tan's lab functions as a centre for sequencing different strains, seeks mechanisms of drug resistance, of how this bacterium comes to infect humans, and how pathogens evolve in the context of humans including their cultural behaviours. Farmers in

Thailand contract meliodosis from working in rice paddy without shoes and getting cuts in the skin. One solution is to get them to wear shoes.

Meliodosis touches on a more important research paradox—what one sees in hospitals in immuno-compromised bodies becomes bio-available to study disease mechanisms, but what these allow to be characterised are a minor selection of the range of organisms found in nature, clinical isolates. To understand their adaptations or evolutions in different environments, molecular biologists, Tan suggests, have to begin learning from ecologists how to study interactions among bacteria as well as host-pathogen ones.

In the contemporary shift from reductionistic biology towards systems biology, epigenetic interactions, and ecologies, Tan asks: 'Is biology so deterministic that every little feature matters, or is it more sloppy where a lot of events happen but maybe they don't really matter that much' (21/12/2010). This is a biological sensibility quite different from the reigning engineering reductionist one.

Tan is a proponent of small-niche collaborations. Malaria and TB get most of the buzz, he says, but 'there are a lot of very small niche, interesting, diseases, endemic in some areas, that speak to larger biological issues' (21/12/2010).

Gastric cancer is another opportunistic, larger, collaboration Tan has led with labs in Japan and Australia.

> What happens is that other people have related data sets... [and] feel that they haven't eked out as much richness from the data as possible. They contacted us to do this work...and once you have that, then you have larger data sets that you can play with. (21/12/2010)

For the first time, they were able to create a classification of stomach cancers, so that clinicians can know a patient should be treated with one drug rather than another, given a particular genetic profile. Still a discovery study, clinical trials are underway on the basis of these molecular classifications. Tan notes:

> ...it takes a lot of working with the clinicians, with the nurses, as to what is clinically acceptable, how far can you depart from standards of care. And it is things like that that hopefully will allow us to really move the hypothesis beyond just the initial promising discovery stage into something that if it works will have a significant clinical impact on patients. (21/12/2010)

Tan is a member of the Singapore Bioethics Advisory Board, that issues recommendations on emerging ethical issues such as animal–human chimeras, stem cell research, who can give consent for neuroscience research with the cognitively impaired, and clinical trials. Part of the reason the gastric cancer trials were acceptable is because the treatments all are standard of care, and what is being tested is only whether it makes a difference to allocate distinct treatments based on patients' genetic profiles. One still has to negotiate physician preferences. As Tan says, in stomach cancer, there is a lot of physician preference for particular drugs, based

on their particular case load experiences, rather than on randomised trials. Another key issue is local cultural reluctance to participate in trials even with the incentive of free drugs. In Singapore, less than half of eligible patients agree to be enrolled.

In sum, Tan's cross-national disease-specific projects involve ethical guidelines (recursively renegotiated) that involve local communities, multiple professional interests, across medical research institutional structures, and across national epistemic and regulatory communities. The running of multi-sited, Phase III clinical trials, regionally—for instance—will be a task requiring considerable organisational skills to work out indemnity, sponsorship and quality control. Singapore is prevented by law from spending state money beyond its borders for such research. At best, it can try to provide auditing of such trials. Tan, like many contemporary biologists, is involved with the cross-national making sense of large data sets that require new methods and technology as in the gastric cancer study, and at the same time, must negotiate such epistemic and regulatory differences.

Genomics and Regenerative Medicine

> Reprogramming is obviously a two step process; it is a ratio of the donor cell programs and reinstatement of the target cell inscription program And we know that the ratio of a starting cell program is much, much easier than the latter. ***So it is easier to wipe things out than to construct them, …constructing a cell state is not the same thing as maintaining it***.
>
> (Kyle Loh, lab meeting, June 2011)

Stem cell research put GIS and Biopolis on the global stage in 2001, and remains a fast-moving arena of discovery in cancer and tissue regeneration. The third five-year period of Biopolis, with its re-alignment, also comes in the aftermath of a potentially revolutionary breakthrough—the ability to begin to work with induced pluripotent (iPS) cells that may avoid some of the ethical and supply issues of working with embryonic stem cells.

Although celebrity stars in the Biopolis research institutes came predominantly from the UK and the US, the Principal Investigators (PI) there are actually from a vibrant mix of national backgrounds, including Singapore, China, Malaysia, Chinese–American, Korea and India. The trajectories of these PIs provide an access to the complex, layered, and interesting cosmo-politics, educational systems and vocational horizons of the region. This is complemented by the inflow of students and postdocs from primarily China and India, but also Vietnam and Iran, as well as rotations of a few Europeans, Australians and American postdocs.

Such a sea change in migration of scientists across the globe probably has not been seen since the post World War II migration of German and Austrian scientists to energise scientific institutions and training in the US, Turkey, the Soviet Union and Latin America. In those cases, it was often established and mid-career scientists. This time, it is younger PhDs and posdocs, but increasingly mid-career and senior

scientists are also returning to China and Singapore. It is worth directing attention to collaborative mechanisms, scientific mentoring, partnering and exchanges, which help a new global site get off the ground while competing vigorously in global science.

Bing Lim and Frank McKeon have run dual labs, with small lab groups at Harvard, but the majority of their work shifted to Singapore. Jianzu Chen (one of the first generation after the Chinese Cultural Revolution allowed to go to university, and one of the first fifty Chinese graduate students admitted to Stanford) works at MIT and leads the molecular biology portion of the Singapore-MIT Alliance housed under the administrative umbrella of CREATE. Like Hyung at Singapore's National Cancer Centre, Jianzu Chen's team has succeeding in creating a 'humanised mouse' with a full complement of human immune genes. These mice can grow human tumours, a much better human disease model than transplanting tumours into mice whose immune systems must be immunosuppresed and in which the tumours grow more slowly and probably differently. It is a way to study how tumours learn to tolerate or inactivate T cells that initially infiltrate the tumours to counter them, but become inactive. Chen's group works with prostate tumours, Hyung's with liver cancer.

The MIT–Singapore alliance allows graduate students and postdocs to work both in Singapore and Boston. Jianzhu Chen and Frank McKeon, for instance, work in close alliance, sharing a graduate student from India. McKeon also works closely with Lim, GIS mouse knock-out model expert Tom Lufkin, as well as with a new Institute of Cellular and Molecular Biology hire, China-born, US-trained, Wah Xien. Bing Lim, a Malaysian from Sabah, north Borneo by origin, one of the last Columbo Scholarship students to be sent to medical school in Canada, and one of the first PIs recruited by Edison Liu to GIS, trains students who move on to prestigious labs at Harvard or back to positions in China, where he is beginning to develop a collaborative research programme on genetically engineered mini-pigs at the Agricultural University of China.

Science, to some degree, is a series of small worlds in which everyone knows everyone, so a real understanding of workings of science, its cross-cultural socialities, buzz, passion, competitions, and excitement requires an on-the-ground, close-up engagement of players and institutions, interplay of new technologies and computational support, inspirational PIs and lab leaders, and the ability to manage many different backgrounds, skill sets and motivational structures.

Cancer and Tissue Regeneration: A Thin Line?

> 'cancer is a disease of the genome...we can identify
> 'passenger mutations' and 'driver mutations'
>
> (Moni Abraham Kurtakose, Mazumdar-Shaw Cancer Centre, Bengaluru, speaking at the 3rd Annual Congress, International Academy of Oral Oncology, Singapore, 15 July 2011)

One of the key mysteries of biology with huge potential impact on medicine is how tissues repair or regenerate, or go awry as in cancer. The damage that influenza causes, for instance, lies in the damage it triggers in the repair systems of the lung tissue. People die of hyper inflammation of the upper airways, not directly from the flu or the virus; it is what the virus triggers. This is common to a variety of respiratory problems including influenza, SARS, asthma and respiratory syncytial virus (RSV) that kills babies. What is it about adult stem cells of the lung that allows for repair? Can one isolate the adult stem cells of different tissues and find the genes controlled by transcription factors for stemness. This has been done for haematopoietic cells and for spermatagonia, but not for most other tissues that also regenerate. The MIT–Singapore project on the cellular and molecular mechanisms of lung-damage repair has now found a range of stem cells and been able to clone them. The next step is to figure out downstream pathways, in vivo migration and renewal capacity.

Puja Kumar, a graduate student in the Frank McKeon and Wa Xian labs, with shared supervision by MIT Professor Jianzhen Chen, has shown how stem cells that line the airways migrate during repair to damaged sites forming pods of cells the size of the damaged area. That cells, remaining immature as if in preparation for differing roles, can migrate to create new structures is a controversial new idea. The key transcription factor has now been identified but the downstream cascades of factors still need to be worked out. What are the 'homing' mechanisms that migrate the cells? 'Homing?' McKeon grins, 'ok, homing that's fringe stuff already. But I like it. It keeps you thinking. But it is also not out of the realm of possibility' (McKeon, 19 June 2010).

One of the things that the McKeon lab is able to do at GIS that it cannot do at Harvard's Department of Cell Biology is repeated high throughput analysis. At the latter, McKeon has access to only two Illumina sequencers. The GIS has eight and better informatics support. An RNA sequencing experiment cost S$50,000, and to do a series of them far exceeded experimental budgets on NIH grants in the US, McKeon, Xian, and colleagues at the GIS have found all the genes under the control of transcription factors that regulate stemness for a number of regenerative tissues, and have cloned the adult stem cells. Among the cancers, the McKeon and Wah Xian labs work on are precursors to cancer in the fallopian tubes and Barrett's Esophagus, a precursor to esophageal adenoma carcinoma associated with gastric reflux.

The prospect that stem cells (long-term renewal) and cancer (infinite renewal, that is, where something in the healthy long-term renewal mechanism goes awry) might have common properties suggest that cancer research and regenerative medicine may come to be increasingly overlapping fields.

Learning to Reprogramme

> Cloning for example, literally, you take a skin cell to go back to an embryo and make a whole animal out of it. Now we can do it in a test tube, make a skin cell

> become a stem cell. ***So differentiation is not one direction***. I am interested in differentiation moving forward, [and] de-differentiation, moving backwards, the so-called 're-programming.' So that opens up a huge area of scientific questions and industrial biotechnology possibilities.
>
> (Bing Lim, 9 January 2009)

> Within the body there is a very tight epigenetic restriction that skin can't turn into blood, because it would be very disastrous. Right? That is, ***we can do things in vitro, that would be inhibited in vivo.***
>
> (Kyle Loh, in a Bing Lim lab meeting, June 2011)

Instead of 'slash, burn and poison' medical tactics—surgery, chemotherapy, and radiation and surgery—the hope of contemporary research is to learn to work with the body's own repair and regenerative mechanisms. In the early 1960s, Ernest McCullock and James Till at the Ontario Cancer Institute initiated the field of stem cell research. Using a mouse experimental system, they discovered that blood has stem cells, that there are factors that send these cells along different paths of differentiation (red and white cells, and platelets), and that an irradiated dying mouse can be restored to life by injecting such stem cells. In 1996, Ian Wilmut and colleagues at the Roslin Institute near Edinburgh, Scotland, demonstrated that one can clone a mammal from an adult somatic cell by nuclear transfer (demonstrated earlier for frogs by John Gurdon, for which Gurdon shared the Nobel prize in 2012 with induced pluripotent stem cell pioneer Shinya Yamanaka). The sheep, Dolly, lived for six-and-a-half years. Mice, rabbits, horses, donkeys, pigs, goats, cattle, dogs and cats have now been cloned. The cloning process was inefficient—it took 277 attempts to get Dolly, and success rates with mammals continued to be quite inefficient. There are also concerns that such clones are never quite normal. In 2006, the field was revolutionised by Shinya Yamanaka's demonstration at the University of Kyoto that one can turn a skin cell into a stem cell (induced pluripotent stem cells or iPS cells) with four transcription factors. Subsequent iterations showed that one could use other factors and improve the efficiency and speed. The promise is being able to reprogramme (or 'transdifferentiate') somatic cells directly into other tissue types, to get say, blood, or neuronal cells, directly from skin cells.

In other words, there have been three salient advances—the discovery of stem cells (Till and McCulloch), the reprogramming of differentiated cells to totipotency through nuclear transfer (Gurdon and Wilmut), and the reprogramming of differentiated cells to pluripotency through defined factors (Yamanaka). Next steps are to direct reprogramming between differentiated lineages, and to figure out why oocytes reprogramme cells to totipotency more efficiently than defined factors reprogramme cells to pluripotency (iPS cells). Much remains to be specified in all these processes. MicroRNAs have become recognised as an important regulatory system, modifying the more obvious transcription factors that regulate genes. What in the cytoplasm of oocytes makes reprogramming more efficient than iPS factors alone is not understood. Still the idea that differentiation is not one way, that

one can de-differentiate a cell back to a pluripotent state that in turn can forward re-differentiate into any tissue in the body, is a revelation of the past few years.

Bing Lim's GIS lab works on several frontiers (stem cells, iPS reprogramming, microRNAs, cancer, and, with McKeon, lung repair) and has scored a series of high-profile papers. The successes grow organically from Lim's career trajectory traversing the history of the field. His mentor in Toronto, Ernest McCulloch, started the field of experimental stem cell research. Working with McCulloch and Hans Messner at the Ontario Cancer Institute, Lim characterised various progenitors of blood in humans, showing that some make certain kinds of blood cells and not others. Moving to Harvard, Lim worked on how mouse embryonic stem cells differentiate into blood and discovered that the NF-kB pathway has an important role in blood cell generation. He became interested in embryonic stem (ES) cells, and pursued that in Singapore. In trying to make blood from ES cells, he needed to understand the factors underlying pluripotency. In a paper in *Science*, he showed that different types of stem cells express different genes, deflating the prevailing 'stemness' hypothesis that any stem cell can generate all tissue types.[13] Blood stem cells can make only the different types of blood cells; likewise for neural stem cells. It appears, moreover, that an iPS cell, de-differentiated back into pluripotency, can be nudged *in vitro* into other kinds of cells, but always retains a tendency toward, or 'memory' of, the lineage it originally was intended to differentiate into. *In vivo*, so far, such nudging into another cell type has not been accomplished. Finally, while working to characterise a particular signalling pathway, he also discovered a gene that triggers an autoimmune disease like lupus.

Lim notes that the funding and the sequencing facilities provided the opportunity to do things he could never have done at Harvard, while, of course, a few other things are harder to do in Singapore than in the US where there are also private sources of funding. While initially people came to Singapore because of the restrictions in the US on working with embryonic stem cell lines, today research is moving into much more sophisticated technologies. Work with human oocytes is not yet possible in Singapore, while, with private funding, it is in the US. Other things such as Lim's work with micro-RNAs and reprogramming got GIS intramural funding and Lim recruited students who had experience with nuclear transfer. There is no way, he thinks, he could have gotten NIH grants to pursue these initiatives without already having preliminary data. So the funding allows new lines of investigation to be tried much more easily.

The debate about funding organisational mechanisms that foster creativity and innovation is perennial, and NIH's peer review system is often faulted by scientists as overly conservative. Many senior scientists casually talk about how you always start new lines of research on money from older project grants for which you could not get money directly, and then if they pan out, you repay yourself with grants you write on the basis of work already done. For oocyte work, there are other, regulatory, issues. Since oocytes reprogramme differentiated cells more efficiently and completely than the defined factors used to produce iPS cells, they remain an important resource for stem cell research.

> Up until the Yamanaka experiment, nuclear transfer was the best way to potentiate from your skin, reprogram inside the oocyte and then pull out the embryonic stem (ES) cells. Now we just take the skin cell, put in the four gene factors and get to the ES cell.[14] But we know already that the quality of this [the latter] is not as good as this [the earlier method], definitely not as good. In the end, what we want to understand is what is so important about the oocyte environment... You can do it in pigs and so on. But in humans it is very difficult. (Lim, 9/1/09)

While in the US, there is no barrier for private companies to give money to oocyte donors, as long as no federal funding is involved, in Singapore allowance is made only for patients already undergoing tubal ligation. From a science point of view, Lim thinks the work with oocytes will prove to be important for resolving the difference between embryonic stem cells derived from oocytes and with transcription factors (iPS). 'The quality is definitely different. Not only that, the process is different. With the oocyte it is done in forty eight hours. Using this [Yamanaka] method, it is a slow gradual process over ten to fourteen days. So biochemically there is a distinct difference' (Lim, 9/1/09).

On the other hand, in addition to funding, equally important were the sequencing facilities at GIS and the ability to put computation and systems biology together. The microRNA work for example provides a model. Many algorithms can be tried to predict what the microRNAs are doing, but the predictions are limited unless you can take it into the wet lab to test. The effort is to map network regulation of transcriptional and microRNA factors. Both in normal cells and in disease, transcription factors and microRNAs bind to many genes, which then regulate other genes in a network of interactions. The iterative process of computational prediction and biological testing is 'particularly important in microRNA because microRNA is very subtle, whereas transcriptional factors can be very strong and very dominant' (Lim, 9/1/09). MicroRNAs change the expression of a gene only 20–30 per cent, which is very subtle compared to a transcription factor which will tell a gene turn on or off. As an analogy, he says, think of a neuronal system and moves his arm up and down, 'if everything is functional you have this smooth movement...Something goes wrong and you have this [arm stutters, stops, starts, still moves down, but not smoothly]. Ok, it still works,...I can still move and take this thing...We refer to it as a sort of 'buffering' (Lim, 9/1/09). MicroRNAs occur in clusters, that is from the same transcript, but do different things, and when isolated, one may be more like an ES cell, another when over-expressed may induce differentiation.

> So separately they do two different things, when the two are together I don't know what it is doing. So it is almost like this motion I was talking about [the stuttering motion of his arm], plus and minus, plus and minus, if you have too much plus it may be like this, too much minus you may be like this. But you need to have the plus and minus. (Ibid.)

In sum, GIS and other Biopolis basic science labs provide exemplars for thinking about the challenges of managers in the Economic Development Board (EDB) and

elsewhere who try to evaluate the role of the basic sciences in the development pipelines, establish metrics of productivity along the way, and hope for therapeutics and economic benefits to come more quickly (see Note 7 and Battelle, 2011). In terms of training students who move on to important labs elsewhere (and can return to Singapore), or high-impact publications, and intellectually in terms of helping to move a fast-paced and dynamic field of biomedicine forward, GIS labs seems stellar. The effort to work with lung cell systems, circulating tumour cells in blood, or other tissue systems by cloning, sequencing, and figuring out the regulatory systems should be of interest to pharmaceutical companies as well as for longer range regenerative therapies. The trick is to bring the different styles of working into new productive relations.

Conclusions

> Scientists are attracted to an ecology of science and reason...money, facilities, and resources, but there also needs to be good students, rational governance, and management by a science-knowledgeable leadership...and good living conditions.
>
> (Edison Liu, 2011)

1. Experimental Platforms, Turmoil and Transitions

On 15 December 2011, the Genome Institute of Singapore held a gala dinner to mark the passing of the leadership flame from founding director Edison Liu to Singaporean stem cell-biologist Ng Huck Hui. Liu was moving on to become the President and CEO of the Jackson Labs in Bar Harbour, Maine, the first non-mouse biologist to lead that institution in its own transition towards human genetics and diseases, with a new genome centre in Connecticut and a new consortium partnership with the Memorial Sloan Kettering Cancer Centre in New York. Among his plans are a move into Asia beginning with hopes to link GIS and Jackson. Jackson's chief scientific officer, information technology officer and facilities director visited GIS at Liu's invitation the two previous days. Liu takes along with him one or two principal investigators, including Ruan Yijun, one of the key players in the SARS story. The Liu and Ruan labs, with about ten persons each, helped with the downsizing of GIS to meet the financial reorganisation mandated by A*STAR. Several other PIs also left. Over the following painful two years, GIS (along with other Biopolis institutes) learned to seek out new collaborations with industry and clinicians. By 2013, new funds had begun to flow in. Just how GIS continues to negotiate this realignment and what it means in terms of the future place of basic, industry-aligned, and clinical research will be on the evaluative agendas of all parties involved.

Meanwhile, if as indicated, Biopolis is one piece in a larger experimental decision-making and design platform or ecology, we must look to changes that are occurring elsewhere in the universities and other research institutions, including

the new facilities for CREATE intended for a thousand researchers, and currently the umbrella for alliances with eight international universities. Certainly, as Edison Liu points out, the living environment is also part of this experimental platform, and Singapore as a city and a venue has been changing its built environment dramatically, not always with the full enthusiasm of citizens who made their views—about housing prices, foreign competition in the labour market, and other practical matters—known in the May 2011 elections, but who are inherently part of the larger bio-polis with accents on both syllables.

2. Biological Sensibilities: Infection, Socialities, Regenerative Reason

I have attempted to use three signature arenas of work at the Genome Institute of Singapore—infectious disease; science diplomacy; and regenerative medicine—as probes into wider partial successes and on-going challenges in the biosciences and biotechnologies in a period when they are ascendant as the lead sciences of the day, yet under financial cut-backs and redirection. Financial constraints brought a number of 'whales' (international name scientists) to Singapore in the early 2000s. Some have now left, but others still come. For a younger cohort, we are witnessing one of the largest migrations of young scientists across the globe from East to West, and as 'turtles' back East since World War II.[15] While this article has not tried to numerically characterise these flows, I have attempted to direct attention to the *cultural arbitrage* and *science diplomacy* (the one more competitive, the other more collaborative) across uneven terrains of opportunity, access, funding, expertise and trust that operates in attracting scientific talent, negotiating collaborations in niche disease arenas as in global pandemic responses.

One of my themes has been to attend to the breakdown of trust and repair mechanisms: in the use of the Internet to get governments in China and Hong Kong to reveal what was happening to the public (for example, *sosick.org*); in the forced culling of backyard chickens in Indonesia when the problem was elsewhere; in the refusal of Indonesia to share avian flu samples because they would not benefit from the results; in the CDC restrictions on exchange of melioidosis strains; in the dependence of researchers on clinicians and nurses (gastric cancer trials, liver cancer trials) for what is clinically acceptable variation in standards of care to try something new; in the establishment of the Pan-Asian SNPs Consortium and the Human Genome Organisation to create *networks of* people who trust one another based on prior working together, and *models for* knowing how to build such trust for future emergencies and collaborations.

Trust and what I call the 'peopling of technologies' within institutions as well as across them—making the difference between those that work and those that constantly break down—are but a part of a culturally emergent biological and ecological sensibility. This 'sensibility' (active sensing and responsiveness, not merely intellectual knowing) is signalled in such terms as biorepair, bio-shields, ecology, the biome, permeable membranes (as a policy concept), green technologies, greening of cities, regenerative medicine, and personalised medicine. It is

also signalled in increasing attention to building ecologies of expertise—what it takes to build new robust communities of science that play on the global stage and are innovative locally, both grooming talent and giving back to the community. In pushing back against the Economic Development Board's narrow measurement of key performance indicators, Edison Liu points out:

> I think the billions we have spent have already delivered. Those who question what Singapore got for its investment ignore how companies along the complete spectrum of life sciences, from devices to pharmaceuticals, to hospitals, now make Singapore their Asian home. Clinical and basic biological research are both critical for this industry to flourish, but like quality secondary schools or excellent public transport, the direct accounting of their contribution to the GDP (gross domestic product) is near impossible. (Liu, 2011, quoted in Chang, 2011b)

From the opposite side of the policy debate, A*STAR chairman Lim Chuan Poh indeed also counts the setting up of multinational labs by Abbott, Roche, GlaxoSmithKline, and Proctor and Gamble as positive results of the A*STAR investment (*The Straits Times*, 27 September 2011, A26). Their difference lies in the perennial disagreements about whether science can be directly managed to produce economic outcomes, or whether to over harness the serendipity of scientific discovery is self-defeating. As Liu puts it, 'There is a strong commitment to science here [Singapore] and great research, but there is also a tendency to over plan, thinking incorrectly that we can predict success in scientific discovery' (Liu, 2011). At issue is understanding enough of the basic science to be able to distinguish between aspirations and pragmatic pipelines of experimentation, what is a breakthrough and what is just normal science, and what is to be expected from basic science versus 'industrially aligned' science. At issue is the 'polis' part of *bio-polis*, the deliberative mechanisms of science management.

In 2011, GIS scored the largest number of high-impact publications among the Biopolis institutes, and the four founding GIS stem cell scientists won the President's Science Award—Bing Lim, Ng Huck Hui, Paul Robson, Lawrence Stanton—citing both basic biology and translational applications.

3. Bio and Polis

This article, as noted above, is a partial account as seen from the general perspective of life scientists within A*STAR's Biopolis, rather than say from a clinical researchers' perspective with the hospital systems or from pharma or industry's perspective.

This article has argued that enough of the basic science must be unpacked to be able to see the social processes involved in the construction of creative and innovative new life sciences communities. A key driver is the intense interest in the promise of the life sciences not simply to provide more medicines but to provide insight into the repair mechanisms within biologies and their habitats, to work with rather than against nature.

Singapore, the Genome Institute of Singapore, and the Human Genome Organisation have provided me with a model system or model organism to think about science diplomacy and social infrastructure development across national competitiveness and mistrust; about alternative institutional organisational forms in an ecology that is both nation-building and cosmo-political; and about the ways laboratory science and field sciences such as anthropology and urban planning articulate inside and outside the laboratory walls, as communities of concern, technoscientific imaginaries, and creative, innovative and reflexive social organisational forms. These are creatively renewed in spaces such as trade shows (as ethnographic spaces where corporate and academic practices awkwardly interface), conferences (as competitive spaces), ethics rounds (where intractable dilemmas and procedures are recursively and reiteratively deliberated), lab meetings, and regulatory decision-making spaces. Above all, I am constantly impressed by how articulate and thoughtful people are in their technological lives and about the scientific arts that are part of those lives, but how reduced discourse becomes in the so-called public sphere. One of the promises of a biological sensibility, in the sense I intend here, is a gradual increase in the ability of the public to talk about matters that concern the bios as well as the polis of us all.

NOTES

1. Lim Chuan Poh, Chairman of the Agency for Science, Technology, and Research (A*STAR), writing in *The Straits Times* on 27 September 2011 gives the following figures: biomedical science R&D (research and development) funding through A*Star for 2000–2005 was $1.3 billion; for 2006–2010, it was $2.1 billion; and for 2011–2015, it is $2.3 billion. Of the last amount, $600 million or 26 per cent has been put into a competitive Industrial Alignment Fund, and 30 per cent of this ($180 million) has been awarded to forty-three projects and eleven technology platforms. Biomedical science manufacturing in the period 2000–2009 tripled from $6 billion to $21 billion; employment doubled from 6,000 to 13,000; and employment in R&D from 2,2500 to 5,000. On efforts to calculate the economic impact of the Human Genome Project, see Battelle (2011) and Drake (2011).
2. In Guangzhou, at the time of the SARS outbreak, Number 8 People's Hospital had no ICU (intensive care unit), no central oxygen supply system, no negative pressure wards (Shan and Jiang, 2013).
3. For a slightly different account, emphasising Hong Kong's role, downplaying Singapore's, and stressing the smooth cooperation among global labs, see Chan-Yeung and Christine Loh 2004, 45–58. A well-known phenomenon, histories are also matters of national competition. In a gentle review of the version focused on China, Alain Guilloux notes (2007) that Alan Shnur, a WHO team leader in Beijing, gives a 'tactful account' and 'carefully avoids highlighting the fault lines, tensions and conflicts that paved the road to disclosure by the Chinese authorities'. Jian Wang's Beijing diagnostic company, now owned by GBI, once given access to samples, also made an early diagnostic kit in early April 2003 (Jian Wang, interview on 9 April 2013).
4. The genetic origin was traced eventually to a descendant of the triple-re-assortment virus that emerged in factory farms in the US in 1998. The role of industrial production of chickens in China and Southeast Asia similarly has been hypothesised as a cause of the avian flu rather than wild birds. Although the fatality rates were not as high as initially feared, some 17,700 deaths have been attributed to the strain worldwide (Wikipedia).
5. Chan-Yeung and Loh (2004, pp. 45–48) provide a description of WHO virologist Klaus Stohr's establishment of an emergency-secure website and daily conference calls among thirteen labs

across the world. They highlight the work of the Hong Kong labs of Peiris and Chan Kwok-hung at Queen Mary Hospital in seeing the virus in culture, of Hong Kong University pathologists Wilinia Lim and John Nicholls in using an electron microscope to observe the virus, and Hong Kong University researchers Guan Yi and Leo Poon Litman in piecing together a partial genetic fingerprint, rapidly confirmed by labs in Atlanta and Hamburg, Key next steps were by University of California at San Francisco (UCSF)'s Joseph DeRisi in detecting the novel form of this coronavirus and Rotterdam's Erasmus University labs in infecting monkeys with a 'SARS associated' virus to confirm, according to Koch's postulates, that it was the single causal agent. They don't say that full sequencing of different strains was then done in Vancouver, Atlanta and Singapore, allowing diagnostic kits to be designed in Singapore and commercialised by Roche.

6. For an interesting novelistic account of the fear on the ground in Beijing among the middle class public, see Hu Fayun (2011).
7. China had the largest number of deaths (349), although a much higher number of probable cases (5,328) according to WHO, resulting in a relatively low-case fatality rate of 6.6 per cent, while Canada's was the highest at 18 per cent, followed by Hong Kong at 17 per cent (of 1,755 probable cases), and Singapore at 14 per cent.
8. While Koch's four postulates do not universally hold, as he himself pointed out (not all exposed organisms fall ill), they provide a framework for establishing causality. The microorganism must be found in all sick organisms, they must be grown in pure medium, then introduced into a healthy organism, and then isolated from newly diseased host organisms and clearly identified with the original causative agent.
9. Malik Peiris' lab at the University of Hong Kong was the first to announce on 21 March 2003 that a new coronavirus might be the cause of SARS after successfully cultivating it from tissue samples and was also among the first to develop a test for the presence of the virus.
10. Migration studies, of course, are also politically charged. The conclusion of the HUGO Pan-Asian SNPs Consortium study was to support the 'one wave' theory of migration into Asia, which follows the gradient of greater genetic diversity in Southeast Asia towards the north. But many in northern Asia have been invested in a two-wave theory, one from the south and one across the north, and there was at least one angry response from a Korean scientist in the 'Letters' section of *Science*, complaining of the small sample size and other limitations.
11. Quoted in Chang Ai-Lien (2011a).
12. This is not the place to track all the IRB and ethics committee safeguards involved here in this early scientific discovery process, only to note that Singapore has and continues to develop these quite carefully (Kaan and Liu, 2006).
13. In 2011, Kyle Loh and Bing Lim proposed an alternative to the prevailing model of stem cells in a stable ground state inhibiting differentiation.
14. 'Embryonic stem cell' is used interchangeably for the iPS cell (de-differentiated back to pluripotency) and for the pluripotent inner cell mass of the blastocyst produced by the fertilised ooycte.
15. *Haigui*, sea turtle, is slang for Chinese who return from studying abroad. It is a pun from its two characters: *hai* (water), *gui* which is a homophone for 'to return'.
16. For a fuller reference list, see author's website.

REFERENCES[16]

Battelle Technology Partnership Practice (2011). The economic impact of the Human Genome Project. Retrieved 29 May 2013, from http://battelle.org/docs/default-document-library/economic_impact_of_the_human_genome_project.pdf

Chan-Yeung, M. and Loh, C. (2004). The new coronavirus: In search of the culprit. In C. Loh (Ed.), *At the epicenter: Hong Kong and the SARS outbreak* (pp. 43–54). Hong Kong: Hong Kong University Press.

Chang, A.L. (2011a, 21 June). Special mice help prove drugs work on cancer victims. *The Straits Times*, A8.

Chang, A.L. (2011b, 7 September). Returns not always about money, says Star Scientist. *The Straits Times*, A 14.

Chua, B.H. (2006). SARS epidemic and the disclosure of Singapore nation. *Cultural Politics*, *2*(1), 77–96.

Clancey, G. (2012). Intelligent island to Biopolis: Smart minds, sick bodies and millennial turns in Singapore. *Science Technology & Society*, *17*(1), 13–35.

Drake, N. (2011). What is the human genome worth? *Nature*. Published online, 11 May 2011, doi: 10.1038/news.2011.281.

Guilloux, A. (2007). Review of Arthur Kleinman and James L. Watson (Eds) SARS in China. *China Perspectives* [Online]. Retrieved 29 May 2013, from http://chinaperspectives.revues.org/1923

Hu, F. (2011). *Such is this World @ sars.com*. Dobbs Ferry, NY: Ragged Banner.

Kaan, T. and Liu, E. (2006). *Life sciences: law and ethics: Recent developments in Singapore*. Singapore: Singapore Academy of Law and Bioethics Advisory Council.

Khor, M. (2007, 20 February). Indonesia to share bird-flu samples only if there is a new system. *Third World Network*. Retrieved 29 May 2013, from http://www.twnside.org.sg/title2/avian.flu/news.stories/afns.002.htm

Koh, B.S. (2011). *Brand Singapore*. Singapore: Marshall Cavendish.

Latour, B. (1988). *The pasteurization of France*. Cambridge: Harvard University Press.

Leung, G.M., Quan, S., Ho, L.M., Ho, S.Y., Hedley, A.J., Lee, H.P., et al. (2004). A tale of two cities: Community psychobehavioral surveillance and related impact on outbreak control in Hong Kong and Singapore during the severe acute respiratory syndrome epidemic. *Infection Control and Hospital Epidemiology*, *25*(12), 1033–1041.

Lim, C.P. (2011, 27 September). Singapore's biomedical push. *The Straits Times*, A26.

Liu, E. (2011, 7 September). Quoted in Chang (2011b).

Lowe, C. (2010). Viral clouds: Becoming H5N1 in Indonesia. *Cultural Anthropology*, *25*(4), 625–649.

Ong, A. (2007). *Neoliberalism as exception: Mutations in citizenship and sovereignty*. Durham: Duke University Press.

——— (2010). Lifelines: The ethics of blood banking for family and beyond. In A. Ong and N. Chen (Eds), *Asian biotech: Ethics and communities of fate* (pp. 190–214). Durham: Duke University Press.

——— (2013). A milieu of mutations: The pluripotency and fungibility of life in Asia. *East Asia Science Technology and Society: An International Journal*, *7*(1), 69–85.

Reardon, J. (2005). *Race to the finish: Identity and governance in an age of genomics*. Princeton University Press.

Shan, J. and Jiang, X. (2013, 28 February). SARS hero reflects on lessons learned. *China Daily*.

Sparke, M. and Anguelov, D. (2011). H1N1, globalization and the epidemiology of inequality. *Health and Place*, *18(*4), 726–36; doi: 10.1016/j.healthplace.2011.09.001.

Tan, C.C. (2005). Public health response: A view from Singapore. In M. Peiris, Larry J. Anderson, Albert D.M.E. Osterhaus, Klaus Stohr and Kwok-yung Yuen (Eds), *Severe acute respiratory syndrome* (pp. 139–163). Oxford: Blackwell.

Tan, W. (2013, 19 March). Warning against complacency, 10 years after SARS. *Today*, 1–2.

Tay, J., Ng, Y.F., Cutter, J.L. and James, L. (2010). Influenza A (H1N1-2009) pandemic in Singapore—Public health control measures implemented and lessons learnt. *ANNALS Academy of Medicine Singapore*, *39*, 313–324.

Waldby, C. (2009a). Singapore Biopolis: Bare life in the city-state. *East Asian Science, Technology and Society: An International Journal*, *3*(2–3), 367–383.

——— (2009b). Biobanking in Singapore: Post-developmental state, experimental population. *New Genetics and Society*, *28*(3), 253–265.