Biotech Highlight

Singapore R&D and globetrotting

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Worldwide, people are setting up or expanding into new careers, universities, institutes, and centers. This situation is particularly good for Singapore. From a biomedical perspective, three main movements may be observed: (1) pharmaceutical, biotechnological and supply companies establishing local-based subsidiaries, (2) renowned universities and colleges establishing biomedical and chemical biology institutes, and (3) researchers of international standing taking the lead to bring-in, train and sustain a first-class local workforce [1, 2].

By discussing the integrative nature of chemistry and biology, we shall attempt to address both local and international perspectives. We shall give an overview of the funding structure and collaborative opportunities in Singapore. As a theme, we have focused on drug discovery. For relevant complimentary information, please also refer to the Singapore special in BTJ's November 2007 issue [3].

1 Feeding research

As with most countries, the national challenge is to transplant fundamental discoveries into the local industry by connecting researchers at differing ends of the discovery-economic matrix. For this to occur, a government needs to pump sufficient money into research and development (R&D), and balance both private and public sector investments. Today, more than ever, this funding for R&D faces an uncertain future. Despite this worldwide concern, Singapore is committed to spending S$40 billion (Singapore-dollars) on R&D before 2010, two-times that spent between 2001 and 2005 [4]. Amongst the R&D strategies described herein, this commitment may be recently highlighted by the official opening of Fusionopolis on October 17th 2008, 5-years after the opening of Biopolis. Whilst the latter is known to house biomedical research, the 30-hectare Fusionopolis complex aims to house 2400 researchers in the chemical, physical, engineering, technological, digital and media sciences by 2012.

So who feeds R&D in Singapore? Together with the Economic Development Board (EDB) to support incoming and local spin-off companies, there are four main funding bodies: the ministries of education (MoE) and health (MoH), the Agency for Science, Technology and Research (A*STAR), and the National Research Foundation (NRF). These government bodies are, in fact, close companions with flexible funding schemes that strategically fund the curiosity-driven, basic, applied and translational research between the universities, graduate schools, hospitals, institutes, research consortia, and industry (Fig. 1). Arguably, this is an internationally unique dynamic; for example, A*STAR recently set up the Cross Council Office (CCO) in late 2007 to stimulate research collaborations between its biomedical (BMRC) and science & engineering (SERC) wings. No doubt this is with a view to streamlining the impending move of most of the

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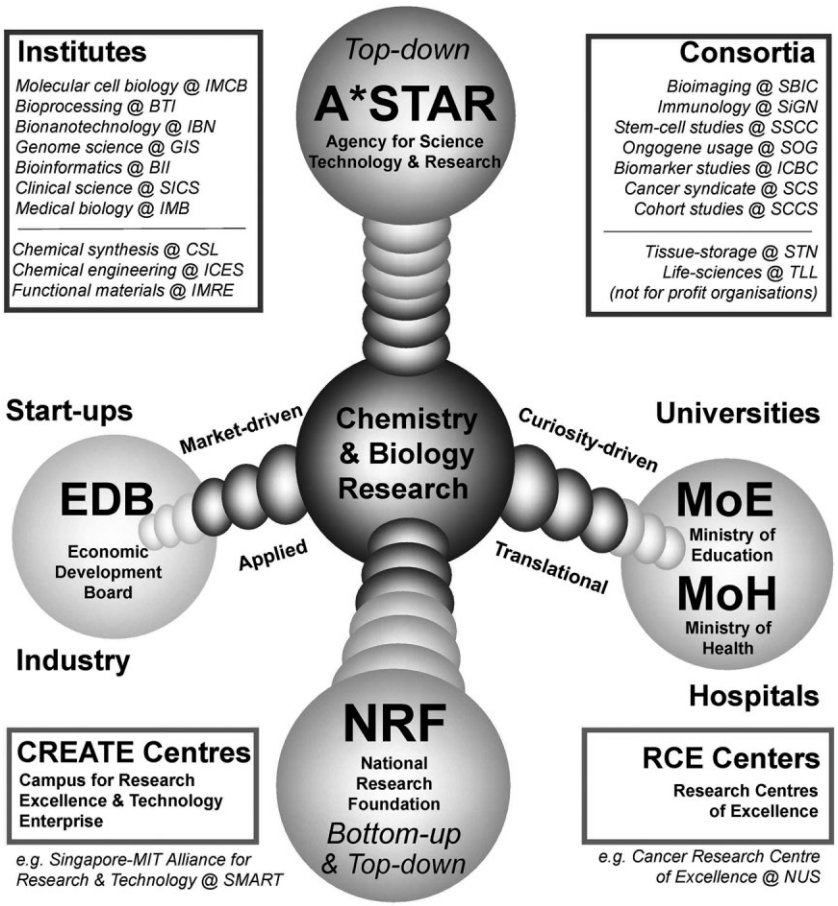

Figure 1. Feeding you, feeding me: chemistry & biology funding in Singapore. Various funding bodies, selected institutes and consortia, and how they integrate with industries, hospitals and universities are illustrated.

SERC research institutes to Fusionopolis, where they will become close neighbors to the BMRC laboratories at Biopolis.

As a city-state, the collaborative avenues amid the Singaporean landscape are fairly amenable to adaptation. Yet, in comparison to the majority of UK, European, Japanese and USA agencies, the Singapore cogs of hierarchy and funding tend to turn more slowly and strategically (vide infra). To be fair though, the more speedy processes of well-established countries have taken many cycles of administrative streamlining.

The thrust from the government is clear: create competition, generate better proposals, bring in talent, produce better science, and make sure it pays off. The 3-year old NRF agency, for example, has established the Campus for Research and Technological Enterprise (CREATE), thereby pushing the universities to head-hunt for program and research directors of potential centers of excellence (Fig. 1). The Cancer Research Centre of Excellence (RCE) has already been set up for translational medicine under the directorship of Daniel Tenen, originally from Harvard Medical School.

The bottom line is that Singapore is bucking the global economic trend and is still actively looking for research talent.

2 Molecular and scholarly pursuits

A reason for Singapore's apparent rise in international recognition is perhaps due to the timely formation of research-training platforms with pedigree partners from overseas. In fact, this was recognized as early as 1998 when MIT and two local universities formed the Singapore MIT Alliance (SMA). A recent notable example is the A*STAR Chemical Synthesis Laboratory (CSL @ Biopolis) that is directed by K. C. Nicolaou and principal investigator, David Chen, who was headhunted from Merck & Co in the United States.

Since its launch in November 2005, the CSL has attracted over 35 graduate and postdoctoral workers into the world of total synthesis and chemical biology [5-7]. Such research and training is vital to drug discovery, namely in the lead identification [8] and chemical synthesis [9, 10] of natural products

[11]. Fig. 2 depicts the multi-faceted ways to connect and derive the most useful biological information out of molecules, the common denominator being the overlap between chemistry and biology [12, 13]. Perhaps paradoxically, the collaborative mixing of fields is not a matter of dilution, but rather a matter of concentration, whereby researchers within each field can give a more robust understanding in bio-discovery [14, 15]. This mixing of fields is quite evident in the awardees of the 2008 Nobel Prize in chemistry, namely Osamu Shimomura, Martin Chalfie and Roger Y. Tsien "for the discovery and development of the green fluorescent protein, GFP" [16].

Another A*STAR laboratory adept in the applications of chemical synthesis is headed by Christina L. L. Chai who joined the Institute of Chemical and Engineering Sciences (ICES) from the Australian National University during 2004. Both David Chen and Christina Chai emphasize chemical synthesis as a dual platform to train researchers and provide valuable tools for biomedical research. They further advocate the importance of countries to provide adequate funding schemes for basic research in the chemical sciences.

In fact, chemical synthesis and chemistry are blossoming in Singapore. It has now been 80-years since the Department of Chemistry found its roots in the National University of Singapore (NUS). Andy T. S. Hor, the founding president of the Singapore National Institute of Chemistry (SNIC) and current departmental head, comments "chemistry is the only compulsory subject in schools, and NUS chemistry has grown to over 60 research staff over the last 80-years". Barry Halliwell, known for his seminal work on free radicals and antioxidants, takes education and research equally seriously. Speaking as the executive director of the NUS Graduate School for Integrative Sciences and Engineering (NGS), he comments "NGS has developed an innovative curriculum that also includes the training of scholars in research ethics and integrity". Furthermore, Nanyang Technological University (NTU) established a Chemistry and Biological Chemistry (CBC) division during 2005, and officially opened a new facility for the molecular sciences during December 2007, modeled after the Oxford Chemistry Building in the UK. Amongst the growing local and international faculty at NTU, the division head Teck-Peng Loh comments that the new chemistry facility and the recruitment of Koichi Narasaka and his group from the University of Tokyo have "attracted worldwide attention".

3 Research clusters

Countries clearly attempt to cluster researchers with complimentary fields of study into one building, so as to share facilities and expertise towards

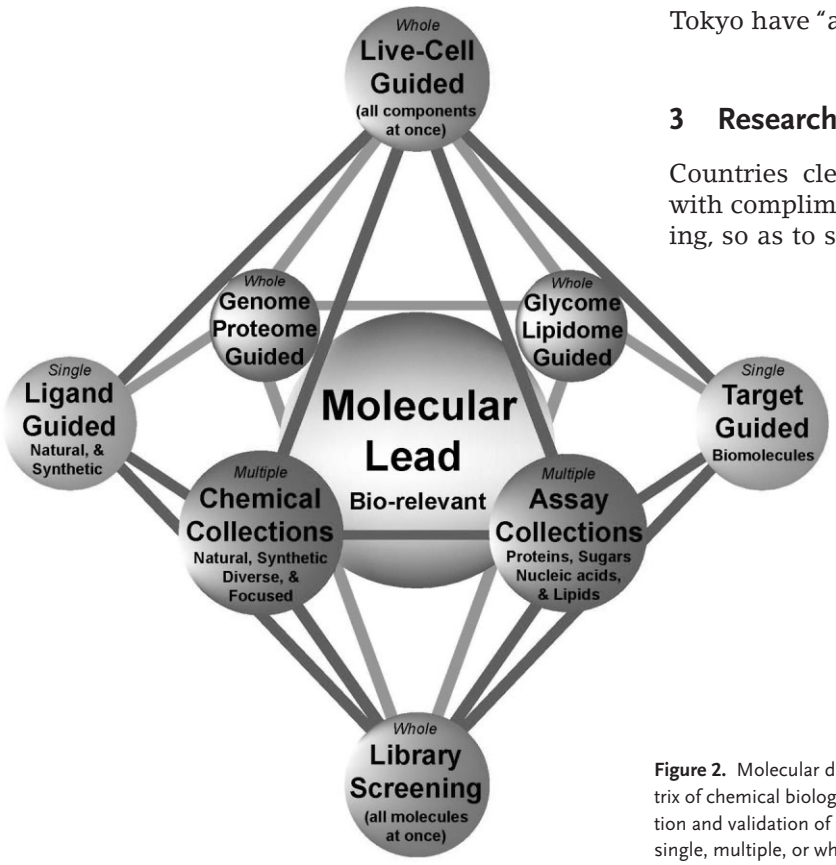

Figure 2. Molecular discovery of active leads. Represented is a modern matrix of chemical biology approaches that allow for the concerted identification and validation of bio-relevant, ligand-target interactions through the single, multiple, or whole-based screening of molecular components [5-15].

specific goals. For example, the Life Sciences Institute (LSI) of NUS has formed the Medicinal Chemistry Program (MCP), an experimental therapeutic platform that bridges the departments of biological sciences, chemistry and pharmacy. The MCP is currently headed by Young-tae Chang, originally from New York University, where he developed his Diversity Oriented Fluorescence Library Approach [17] and a tagged library approach [18] to facilitate chemical genetics. As a continuation of this work, he has also joined the Singapore Bio-imaging Consortium (SBIC) and commented on "a large collection of partners ready to collaborate right at your door step".

A further two new centers for Singapore include the LSI Center for Life Sciences (CeLS) and the new Experimental Therapeutics Center (ETC). The new CeLS building at NUS is home to several groups that target cancer, cardiovascular biology/angiogenesis, immunology, and neurobiology/ageing. As two of the 450 researchers that are filling the CeLS building, Paul A. MacAry and Michael Kemeny, both UK-based immunology and allergy experts recruited over 3-4 years ago [2], comment the "funding opportunities and start-up packages are quite competitive with Europe and North America". Also residing at CeLS and leading the lipidomic drive in Singapore is Markus R. Wenk, who joined both the NUS Departments of Biology and Biochemistry over 4-years ago from Yale University School of Medicine in the United States [19]. When asked what attracted him to Singapore, he mentioned "the dynamic environment of R&D in biomedicine, which would allow us to rapidly establish our lipidomics initiative". Lipidomics is indeed a growing area (Fig. 3). Diseases including cancer, diabetes, neurodegenerative, and infectious disorders typically involve the functional disruption of lipids, which are typically less understood than protein or nucleic acid interactions [20, 21].

Outside NUS at Biopolis, is the ETC, the brainchild of Sir David P. Lane from the University of Dundee, Scotland, UK, famous for his work on the p53 tumour-suppressor gene. The ETC is being run using the disciplines of a biotech company and aims to take drug discovery to the pre-clinical stage by consolidating assay platforms in high-content imaging, whole genome siRNA screening, and high-throughput antibody screening. Nearby is the Institute of Molecular Cell Biology (IMCB), which, since November 2007, has been under the directorship of Neal Copeland and Nancy Jenkins, originally from the National Cancer Institute Frederick in the United States. At the IMCB zebrafish facility international collaborators may select from over 10 000 genetically marked zebrafish (*Danio rerio*) models to study the way chemicals affect disease development [22]. Locally, for example, IMCB has an agreement to screen the extensive collections of natural products from MerLion Pharmaceuticals, a Singapore-headquartered company focusing on the clinical development of antibiotics and the discovery of new drug candidates from natural sources.

4 Critical delivery and support

Finding a molecular lead is one thing, getting it to target and stay on target is another. This is where drug delivery systems come to the fore. Fig. 4 gives

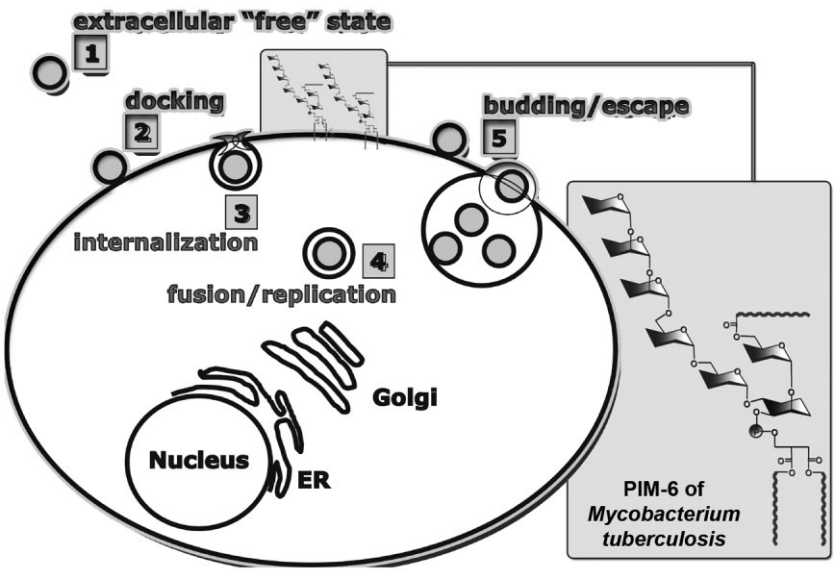

Figure 3. The pathogenic lipidome. Lipidomics is an emerging field in host-pathogen biology that includes the chemical synthesis and the pathogenic detailing of complex phosphoinositide lipids, for example, the phosphatidylinositol hexamannoside (PIM-6) of *M. tuberculosis*.

an overview of the encapsulation technology of a European spin-off company, registered as Austrianova Singapore Pte Ltd during March 2007. Representatives comment that the support mechanisms of EDB were critical for their move to Biopolis and to establishing their start-up projects. Austrianova supports basic research with a long-term applied focus; for example, they recently brought online a unique GMP manufacturing plant for encapsulated cells with cellulose sulphate and founded a Christian Doppler Laboratory (CDL) during August 2007 to combine virology and nanotechnology [23-25] (Fig. 4).

How might this biotech infrastructure compare internationally? Could Singapore do better? Should Singapore ask if their growth outpaces the available resources and manpower? A worry for biotech and translational researchers alike is a lack of support in basic research during the critical years of development between ideas and realization of clinical products. Is this true for Singapore? Such support is critical, especially for the generation of home-grown spin-offs; for example, A*STAR has been known to look internationally for funds to finance their own spin-off companies, thereby suggesting that greater pre-clinical support is needed.

Certainly, government agencies are proactive in helping to raise venture capital and angel investment, at least more than in some other European countries. So, why does it seem that some local researchers still sit on interesting technologies that could and should be commercialized? Agencies such as EDB, Bio-One, Spring and Exploit do work together to find creative solutions and are highly responsive to an applicant's circumstances. Inevitably

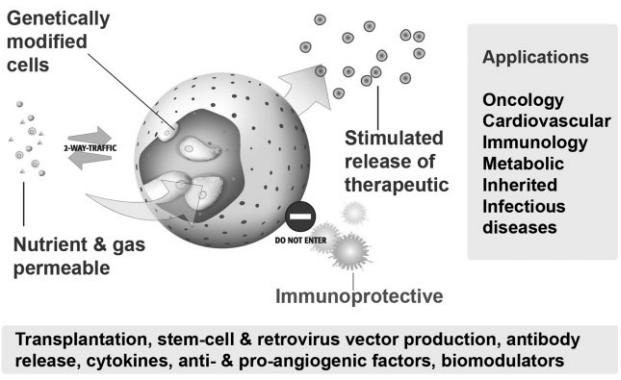

Figure 4. Encapsulating life. Austrianova Singapore Pte Ltd is developing a novel encapsulation technology (NovaCaps®) that has proven its worth in treating pancreatic cancer in phase-I/II clinical trials [24]. A pivotal phase III trial has been planned through protocol advice with the European Medicines Agency.

though, a certain amount of bureaucracy is involved. A common criticism is that financial support is slowly paid out, even though the approval process may be reasonably quick and user-friendly. It may be that administrators are too cautious, require too many people in the administrative loop, or are wary of making mistakes. Both academics and start-up biotechs, who generally live in a hand to mouth situation, may experience difficulties, as a result. Although this problem is not purely restricted to Singapore, there are examples of faster and less bureaucratic disbursement modalities elsewhere.

Not unexpectedly, Singapore negotiates strongly for ownership and commercialization rights on intellectual property (IP), but unusually before any proof of concept or scientific idea has been allowed to be funded or to reach maturity. This may deter internationally-based projects and collaborations. Other Asian countries, notably India and to some extent China, appear to have taken a more relaxed stance on IP ownership and commercialization rights and have attracted considerable interest from pharma companies. The overriding focus should be to attract new projects and collaborations to a country, since the benefits and effects of the success will ultimately be felt there.

By their very nature, start-ups need to be financed up-front and not retrospectively. Indeed, the visionary and father of Biopolis, Philip Yeo pointed this out and this sparked the development of the seed funding agency called Spring that will match every dollar from the company's side to one locally (brought on board usually by an investor). Unfortunately, given the current economic climate, small and new spin-offs and start-ups may increasingly find difficulty in securing sufficient dollars. One alternative could be the provision of a 100% start-up fund to cover the company's initial phases, which would be paid back once a company reaches profitability.

More expeditious and dedicated risk-taking methods are thus recommended for Singapore to become a global player in the biomedical industry and basic sciences, so that more innovative international players can be enticed and persuaded to stay, as well as to encourage more home-grown players onto the scene.

5 Imaging multiple pursuits

As part of the biomedical movement in Singapore is the pursuit of molecular and biomedical probes. The development of new Single-Photon Emission Computed Tomography (SPECT), Positron-Emission Tomography (PET), and Magnetic Resonance

Imaging (MRI) probes is typically a decade-long process and calls for close collaboration between chemists, physicists, biologists, pharmacologists, radiopharmacists, and clinicians: a daunting task for any country (Fig. 5). The key is to gather a cohesive, multi-disciplinary team that understands all the critical steps to clinical development.

Combined with the recent NUS-A*STAR/SBIC-Siemens initiative for a Clinical Imaging Research Center (CIRC) and the new Cyclotron and Central Radiopharmacy Facility (CCRF) of Singapore Radiopharmaceuticals Pte Ltd, Singapore is poised for an imaging boom. The SBIC Chairman, Sir George Radda, who pioneered the clinical use of magnetic resonance in medicine from Oxford University in the UK, comments that "the SBIC has a strong pre-clinical imaging program at its four laboratories at Biopolis, and through its annual grant awards and collaborative opportunities is working with universities, hospitals and research centers to co-ordinate imaging research in Singapore." Through the recently established CCO further bioimaging opportunities between BMRC and SERC are now possible. SERC-researchers such as Su Xiaodi, a surface Plasmon resonance worker at the Institute for Materials Research and Engineering (IMRE), can now work with her BMRC-counterparts at the Genome Institute of Singapore (GIS). Spearheaded by Jonathan Hobley, recruited during 2006 from Tohoku University, Japan, further bioimaging projects [15] have been funded between optics and atomic force microscopy groups at IMRE and Simon Cool and Victor Nurcombe of IMB to image stem cell interactions with surfaces. Notably, Simon and Victor chose Singapore as their base due to the good prospects for commercialization that the island offered.

The next phase with the CIRC initiative is to bring all capabilities into one building with an in-house and dedicated cyclotron and a PET radiochemistry laboratory. Importantly, CIRC will connect directly into purpose built clinics with an initial focus on established MRI-CT modalities, SPECT and PET. Maung Maung Saw, Director of CCRF, emphasizes that the key to the success of this bench-to-bedside imaging drive lies with 'linker' or 'hybrid' scientists. He exemplifies his comments by calling himself a "hybrid" who regularly visits and combines the interests of key specialists, healthcare policy makers and pharmaceutical companies across Singapore. Once operational in January 2009, CCRF will start to produce ^{18}F-tracers, ^{11}C-tracers, ^{13}N-ammonia, second generation ^{99m}Tc-SPECT and therapeutic radiopharmaceuticals.

6 Globetrotting perspectives

Singapore is unique in many ways, but like its past history as a trading post, it has found fortune by virtue of its geographic location. In other words, it is uniquely positioned to be an attractive headquarters for R&D between Europe, Australia, India and other parts of Asia. For example, 'going to the clinic' is a big motive for pharmaceutical companies and medical units to set-up base in Singapore. Regional clinical trial centers include those from AstraZeneca, Aventis, Eli Lilly, GlaxoSmithKline, Merck & Co, Novartis, Novo Nordisk, Sanofi-Synthelabo and Schering-Plough, while clinical services or training (inside and outside Singapore) stem from various hospitals and medical centers, for example, the Duke-NUS Graduate Medical School and the John-Hopkins Singapore Medical Center.

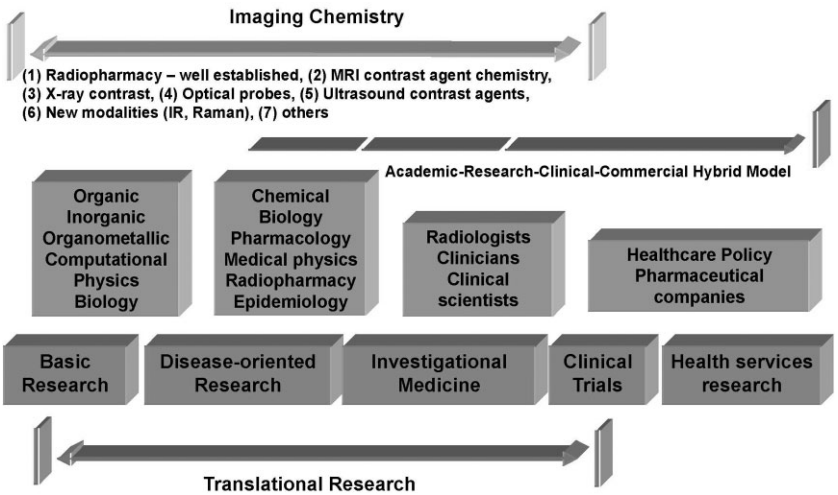

Figure 5. Cross-sectional research strata of molecular and biomedical imaging. A conceptual view on the translation of chemistry and biology into the multi-disciplinary arena of developing clinical probes. Diagram courtesy of M. M. Saw (Cyclotron and Central Radiopharmacy Facility, Singapore Radiopharmaceuticals Pte Ltd, Science Park II, Singapore).

A most recent success story is that of the modest-sized pharmaceutical company, S*Bio, who recently disclosed Singapore's first home-grown small-molecule oncology drug: SB939, a histone deacetylase (HDAC) inhibitor, approved as an investigational new drug for local Phase-I studies by the FDA on 16th November 2007. SB939 is now poised to go into Phase-II clinical trials for hematological and solid tumor patients [26].

The tricky question is: What would be informative to someone who plans to join a new work-place or establish a new scientific division abroad? From our experience, be just as adaptive and dynamic as one's environment. Research-wise, do not be limited by national borders; have the forethought to seek key international partners inside and outside your expertise. As an academic, be reminded that the scientific world is more united for global growth than one might first think. As an industrialist, keep close ties to your international subsidiaries and home base. If possible, seek or set-up a joint or a multiple appointment within the research fields you wish to expand into. For academic, medical, and industrial officials, develop a strong collaborative environment in line with the national strategies and local research institutes. Furthermore, new companies, universities, or institutes would be advised to bring their own staff in for a cross-over period to help invoke local people into your specialist areas.

This commentary is dedicated to the 80th Anniversary of Chemistry and NUS Science in Singapore (1929-2009). In addition to our peers, colleagues and collaborators mentioned above, the authors would like to thank Hilda S. King, James J. La Clair (Xenobe Research Institute, San Diego, United States), Andrew T. S. Wee (Dean, Faculty of Science, National University of Singapore), and Eng-Chye Tan (Deputy President (Academic Affairs) and Provost, National University of Singapore) for their input, encouragement and helpful comments.

This is a non-scientific commentary. Opinions expressed do not represent the official policies of the organizations mentioned herein.

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