"Cosmic Squared" by Marlene Fisher

On the cusp of her successful exhibition at Agora Gallery in NYC Marlene continues to expand the perimeters of her technique and style. The influence of Dali, Magritte and Picasso is evident in her impressionist and expressionist paintings that pay homage to NYC. Her feel for defined linear representation against diffused backgrounds has allowed a welcome transition to her pieces. Recognition of life's beginnings has presented itself in her well received egg series.

BIOTECHNOLOGY IN HONG KONG VOLUME THREE

BIOTECHNOLOGY
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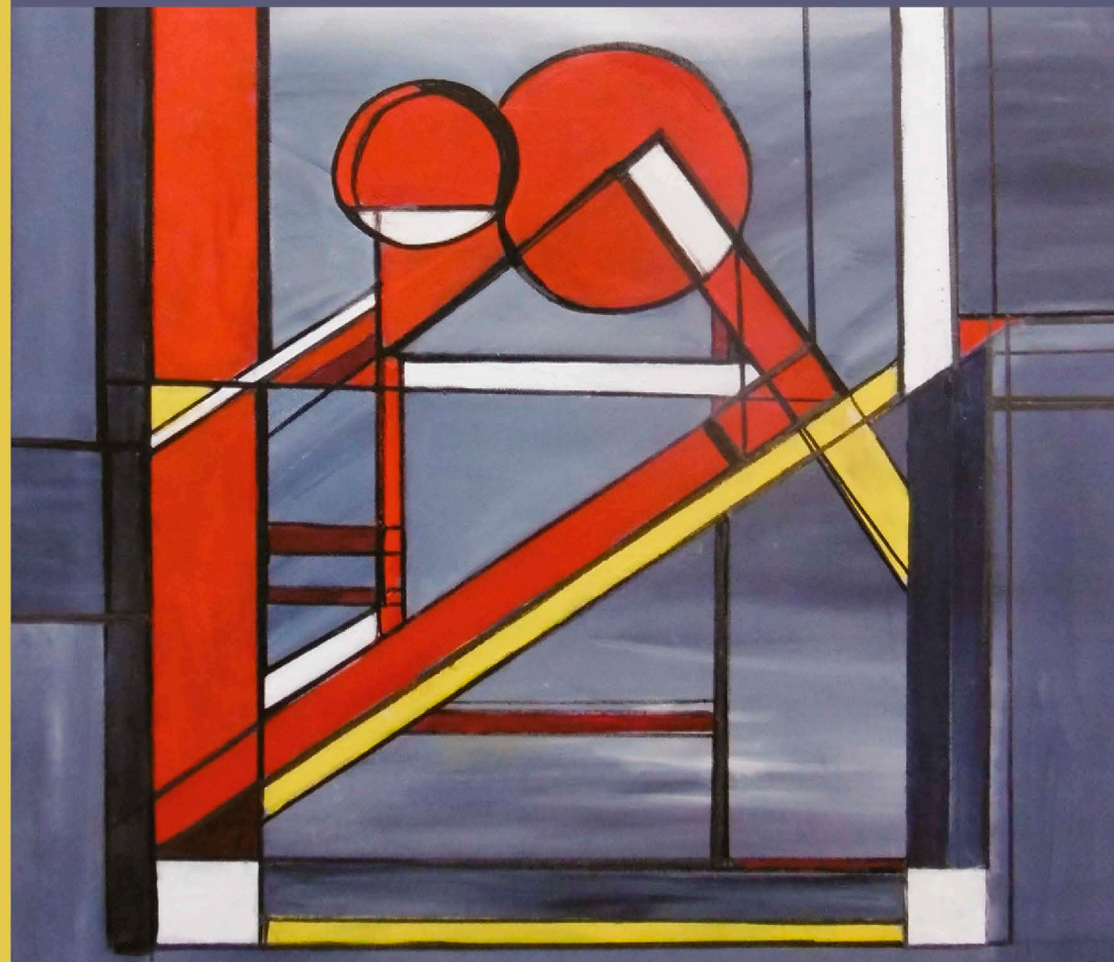

Edited by Albert Wai-Kit Chan, Ph.D., J.D.

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The intention of this book is to provide information only on biotechnology with a focus on Hong Kong. This information is made available with the knowledge that the publisher and authors do not offer any legal or other professional advice. This book does not contain all information available on the subject. This book has not been created to be specific to any individual's or organizations' situation or needs. Every effort has been made to ensure the accuracy, completeness and reliability of the information provided in this book. However, there may be typographical and/or content errors. Therefore, this book should serve only as a general guide and not as the ultimate source of this particular subject. This book contains information that might be dated and is intended only to educate and entertain. The authors and publisher shall have no liability or responsibility to any person or entity regarding any loss or damage incurred, or alleged to have incurred, directly or indirectly, by the information contained in this book.

Editor's Note

Quite happy to let everyone know that volume 3 of Biotechnology in Hong Kong is published. As a continued effort, this compilation of papers serves as an update of biotechnology in Hong Kong, a major hub for business in China. As you may already know, another important hub, Shenzhen, is being considered the new Silicon Valley. It's a reflection of the Chinese market's sustained growth these past few years, as supported by the Belt and Road initiatives. China leads the world on the number of patent applications filings, according to the World Intellectual property Organization. This a great time for biotechnology companies. We have gathered over 20 authors, experts from Hong Kong and abroad, to get their view of biotechnology and how it fits in Hong Kong and China.

As in the previous volume, this one is organized in three general areas: scientific, business/development, and legal. Several articles discuss new emerging research areas that have become prominent these few years, such as diagnostics testing. Other articles discuss the persistent challenges in the development of biotechnology, with all their legal and bureaucratic obstacles, but not without hope. There is always a solution.

I would like to give thanks to the many people for their support; this book exists thanks to the help of multitudes. We at the United States-China Intellectual Property Institute Inc. especially are grateful to our authors for contributing their time from their very busy schedules to help educate and share their knowledge with us. I am also thankful for Ms. Marlene Fisher of the cover design that she painted personally, a wonderfully abstract representation of our theme. Finally, Ms. Julie Lai is the real editor to whom I am grateful.

As a father of three, I am blessed with three wonderful children: Alexandra (19), Christopher (17), and Elliot (9). Of course, my lovely partner for life and great wife, Sharon King Lee. Without their support, this undertaking would not be possible.

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LEGAL

Chapter 1

DEVELOPMENT OF A NOVEL TISSUE-SPECIFIC METHOD TO DETECT CYTOKERATIN 20-POSITIVE CIRCULATING TUMOR CELLS IN METASTATIC COLORECTAL CANCER

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Abstract

Although many studies have shown the vast potential of circulating tumor cells (CTCs) detection in cancer diagnosis and prognosis, our understanding of their clinical significance is still far from complete. A major obstacle arises from the lack of well-established tumor or tissue-specific markers to detect CTCs by immunocytochemical staining after immunomagnetic enrichment (IE). In this regard, we have established the utility of cytokeratin 20 (CK20), a gastrointestinal tract specific marker, for the specific detection and identification of colorectal cancer (CRC) CTCs. This breakthrough was successfully validated in spike-in experiments using CRC cell line models followed by a pilot study which recruited 32 metastatic CRC patients, 25 benign colorectal diseases patients and 27 normal subjects. Results indicated that CK20-positive CTCs were detected in 90% metastatic CRC patients but not in the other 2 groups of subjects using this refined assay. These impressive results have laid the foundation for further development of CK20-positive CTCs e as a promising marker in diagnosis, prognostication and treatment monitoring of metastatic CRC.

Background

Tumors are classified into 2 major categories: benign and malignant. One main difference between benign and malignant tumours is their tendency to metastasize and recur.[1] Before tumor cells metastasize to their target organ, they may circulate in the bloodstream for a short period of time.[1] Therefore, identification of circulating tumor cells (CTCs) can be used to detect malignancy, predict metastasis, evaluate prognosis, assist in the management of cancer patients and monitor for recurrence and metastasis after primary therapy.[1] Two approaches are often used to detect CTCs: 1) molecular-based method to detect a target mRNA expression and 2) cytometric method to isolate and enumerate individual cells.[2] The advantages of the molecular-based method are that it is more sensitive and rapid than the cytometric method.[2] However, it is often criticized for failing to discriminate mRNA expression between CTCs and that from other cell types such as leukocytes and non-tumor epithelial cells present in the patient blood, severely compromising assay specificity.[2] Moreover, the expression of the target mRNA in the cells does not correlate with the actual number of CTCs.[3] On the other hand, cytometric methods currently represent the standard approach for the identification of CTCs because they enable both the morphological examination of malignant phenotype such as nucleus/cytoplasmic atypia (which is impossible with molecular-based methods because cells are lysed to extract RNA) and further characterization on a single-cell level that can help to confirm the malignant nature and invasive potential of the CTCs.[4] On the other hand, weaknesses of cytometric methods include cell loss during the various steps in the immunomagnetic enrichment (IE) procedures, technical variations during manual immunocytochemical staining (IS) and failure of general epithelial markers like broad spectrum cytokeratin (CK) and $BerEP_4$ to provide information on the primary tumor origin of the CTCs which is important for appropriate adjuvant and therapeutic treatment of the patients.[3,5]

1. Despite recent studies having addressed the clinical impact of detecting CTCs in various kinds of cancers, conflicting results continue to emerge which are the results of non-standardized protocols, different reagent kits used, non-specific epithelial markers detected (Table 1). However, the researchers have made an important consensus that cytopathological examination of CTCs after IE with further characterization for their malignant potential, represents a promising approach that may develop into a routine diagnostic test in the future.[2,4,6-8]

Table 1. Abbreviations: CK20, cytokeratin 20; CK, cytokeratin; RT-PCR, reverse transcription-polymerase chain reaction

Types of Cancer	Methodology/ Marker	Volume of blood (mL)	Number of patients	Positive results in patients (%)	Conclusions of study	References
Colorectal	Erythrocyte lysis & RT-PCR for CK20 mRNA	14	100	34	CK20 mRNA is not associated with metastasis.	Wharton RQ, et al. Clin Cancer Res 1999;5:4158-4163.
Colorectal	Magnetic cell sorting & RT-PCR for CK20 mRNA	10	19	26	CK20 mRNA is associated with reduced progression free survival and overall survival.	Hardingham JE, et al. Int J Cancer 2000;89:8-13.
Colorectal	Ficoll-Isopaque & RT-PCR for CK20 mRNA & CEA mRNA	10	52	15	CK20 mRNA and CEA mRNA are not associated with metastasis.	Yamaguchi K, et al. Annals of Surgery 2000;232:58-65.
Colorectal	Ficoll & quantitative RT-PCR for CK20 mRNA	10	99	22	CK20 mRNA is not associated with metastasis.	Giribaldi G, et al. J Mol Diagn 2006;8:105-112.
Rectal	Ficoll & RT-PCR for CK20 mRNA	10	45	Only before endorectal ultrasound: 2 Only after endorectal ultrasound: 24	Presence of CK20 mRNA after endorectal ultrasound has a trend toward a worse prognosis, but this difference is not statistically significant.	Koch M, et al. Int J Colorectal Dis 2007;22:359-365.
Renal	Density gradient separation & RT-PCR for MN/CA9	8	37	49	MN/CA9 mRNA is not associated with tumour grade.	McKiernan JM, et al. Cancer 1999;86:492-497.
Renal	Ficoll + magnetic cell sorting & staining for pan-CK (CK5, 6, 8, 17, 19)	8	59	32	CK positive cell number is associated with tumour grade.	Bilkenroth U, et al. Int J Cancer 2001;92:577-582.
Prostate	Ficoll & RT-PCR for PSA	3	46	22	PSA mRNA does not have positive predictive value.	Thiounn N, et al. Urology 1997;50:245-250.
Prostate	Magnetic cell sorting using Cell Search System for pan-CK (CK8, 18, 19)	7.5	37	62	CK positive cell number is associated with shorter survival.	Moreno JG, et al. Urology 2005;65:713-718.

2. Colorectal cancer (CRC) has the highest incidence of all cancers in Hong Kong (Hong Kong Cancer Registry, 2014). The five-year overall survival rate for CRC decreases with advancing disease stage. The survival rate is 95% for stage I, 87% for stage II, 55% for stage III, and <5% for stage IV.[9] Surgery is the standard treatment for patients with stage I and II CRC, whereas patients with stage IIb (large volume, invasion of nearby organs) and III (nodal involvement) CRC are at a greater risk of recurrence and often need post-operative adjuvant chemotherapy (additional radiotherapy for rectal cancer). Moreover, survival rate improves in those patients with metastatic CRC who respond to systemic chemotherapy, and selected patients with local bowel recurrence or resectable liver metastasis

(or, to lesser extent, lung metastasis) can enjoy long-term disease-free survival after surgery. Therefore, early detection of disease recurrence and metastasis is essential for improving survival.

3. CK20 is a low-molecular-weight cytokeratin that shows restricted expression in the GI epithelium, urothelium, and Merkel cell,[10] and this profile is maintained in malignant tumours of these cells. In surgical pathology, CK20 protein is expressed in 90-95% of CRC cases and therefore CK20 mRNA is considered a useful marker in the detection of CRC in the blood using reverse-transcriptase PCR (RT-PCR) technique.[11-13] However, conflicting results are found (Table 1) which are mainly due to the following factors: a) the transcription of CK20 gene in haematopoietic cells and benign epithelial cells from GI tract, therefore the transcription level of CK20 gene does not necessarily reflect the amount of tumor cells in the blood sample; b) the lack of standardization of the techniques and protocols across laboratories; c) the lack of standardization in the selection of polymerase chain reaction (PCR) primers, the number of PCR cycles and even interpretation of PCR results.[3,14-15] As a consequence, consistent comparison between the studies is difficult, and standardization with automation is urgently needed.

4. Existing prognostic markers of CRC have limitations and more accurate, convenient markers are needed. The widely used serum marker, carcinoembryonic antigen (CEA) is not specific to CRC and is unreliable for the detection of disease recurrence following surgery.[16] Other promising markers such as thymidylate synthase,[17] vascular endothelial growth factor,[18] loss of heterozygosity at 18q[19] and microsatellite instability[20] may be prognostic or predictive of treatment responses in CRC. However, these assays require a tumor specimen, which is not conveniently obtained or attractive to patients because an invasive procedure is required. Imaging modalities such as positron emission tomography scans, magnetic resonance colonoscopy may be useful, but these tests are expensive and not cost-effective for routine post-operative surveillance. Therefore, a non-invasive, cost-effective and accurate detection method is urgently needed.

Development of a novel tissue-specific method to detect cytokeratin 20-positive CTCs in metastatic CRC

The clinical significance of CTCs from patients with tumors is still under debate due to conflicting findings between studies.[21,22] With the rapid technological advancements achieved in the last few years, the detection and analysis of CTCs has become more standardized and reliable.[23] A typical example is CTCs detection and enumeration by the CellSearch System, which has recently been recognized to be capable of providing novel prognostic information that allows a defined stratification of risk of death in metastatic breast cancers.[7] This system uses ferrofluids coated with antibodies against epithelial cell adhesion molecule for epithelial cell capture and antibodies targeting CK8, 18 and 19 for epithelial cell identification.[2] However, the limited anti-CK antibody panel used may account for its low sensitivity and specificity when used in certain cancer types such as liver cancer and nasopharynx cancer. Therefore, we hypothesized that CTC detection and enumeration using a specific marker may reflect the patients' conditions more accurately. In 2005, we detected successfully an especially high level of circulating CK20 mRNA in 33% CRC patients without apparent evidence of metastasis (pN0 in TNM staging system).[24] Subsequently, more than half of those patients were found to develop metastasis in 2007. Based on this evidence, we further hypothesized that viable CK20-positive CTCs are present in CRC patients which may account for their high incidence of metastasis. We then began to design an assay to detect CK20-positive CTCs using IE and IS approach which, at that time, only detected general epithelial markers like broad spectrum CK and $BerEP_4$ and were not specific to any cancer or tissue types. In order to solve this problem of non-specific detection, we blocked the mouse anti-$BerEP_4$ antibody that linked to magnetic beads using a polyclonal goat anti-mouse antibody (Figure 1).

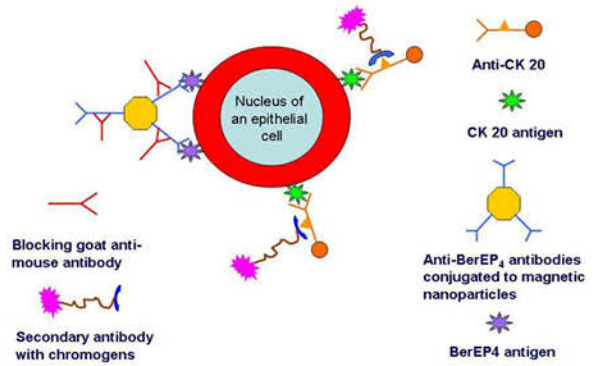

Figure 1: Principle to detect CK20 antigens of an epithelial cell after blocking of the magnetic beads linked anti-$BerEP_4$ antibody

This concept was implemented in the capture of SW480 cells (a CRC cell line) followed by blocking of the mouse anti-$BerEP_4$ antibody and detection of CK20 antigen by IS with anti-CK20 antibody. The results were very impressive because this refined assay not only prevented the visualization of $BerEP_4$ staining, but also exposed the CK20 antigens for staining by anti-CK20 antibody. The successful blocking of the magnetic beads linked antibody has enabled us to detect other tissue specific antigen like CK20. We continued to examine the sensitivity of this novel assay by spiking various quantities of SW480 cells into blood samples from normal subjects where detection limits were found to range from 100,000 to 100 SW480 cells per 10 mL blood. This breakthrough opened up a new avenue for non-invasive cancer detection and monitoring because it potentially allowed detection of all other specific cancer markers in the CTCs after IE. We extended the application of this assay by detecting and enumerating CK20-positive CTCs in 32 patients with metastatic CRC, 25 patients with benign colorectal diseases and 27 normal subjects. We discovered that there was a broad range in the numbers of CK20-positive CTCs (0-377, median = 45 per 10 mL of blood, sensitivity of detection = 90%) in patients with metastatic CRC whereas no CK20-positive CTCs was found in patients with benign colorectal diseases and normal subjects (Figure 2, the intra- and inter-assay coefficients of variance were 3% and 6%, respectively).

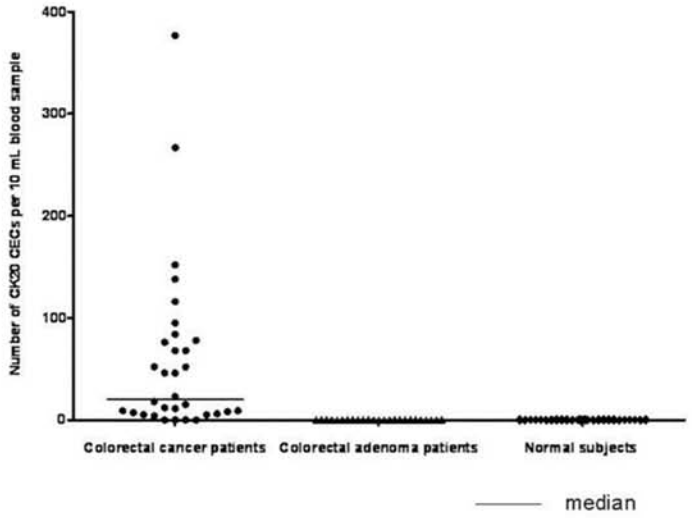

Figure 2: Number of CK20 circulating epithelial cells in 32 patients with metastatic colorectal cancer, 25 patients with benign colorectal diseases and 27 normal subjects. The median is shown by a black horizontal line.

Moreover, we also compared the number of CK20-positive CTCs detected with that of broad spectrum $BerEP_4$-positive CTCs in 10 metastatic CRC blood specimens and discovered that the number of CK20-positive CTCs detected was lower than that of $BerEP_4$-positive CTCs in each of the same patient specimen (Figure 3). These results indicate that CK20 is more specific than the general epithelial marker $BerEP_4$ because anti-CK20 antibody would mainly detect epithelial cells from GI sites and therefore, CK20-positive CTCs may be a promising marker for detecting and monitoring metastatic CRC. With our expertise in developing circulating tumor markers and competence in IS and interpretation,[25-27] our team has laid down a solid foundation for further investigation into the significance of CK20-positive CTCs in metastatic CRC detection.

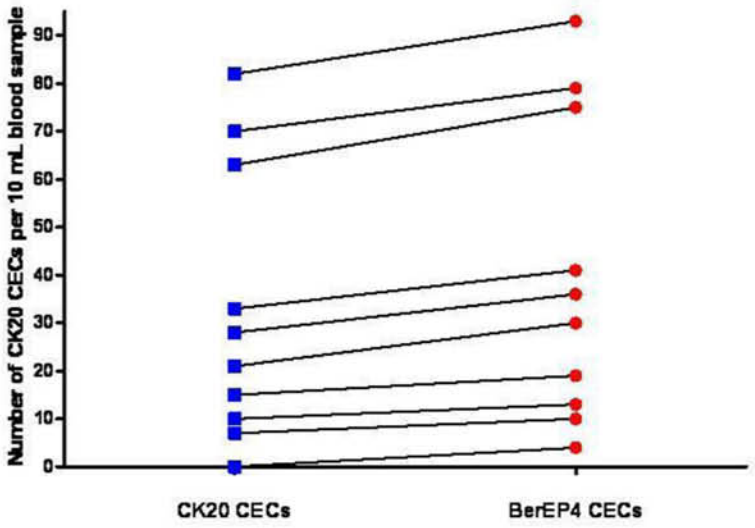

Figure 3: Comparison of the numbers of CK20 circulating epithelial cells with those of $BerEP_4$ circulating epithelial cells detected in 10 metastatic CRC blood samples.

Key issues and problems:

1. Molecular based methods such as reverse transcriptase-polymerase chain reaction (RT-PCR) would destroy the CTCs, making it impossible to count or to analyze them individually. Moreover, the lack of standardized protocols and illegitimate expression of target genes in normal hematopoietic cells limit reproducibility between laboratories and hamper their development into routine molecular tests in diagnostic laboratories.

2. Current IE methods utilize either broad spectrum anti-CK or anti-$BerEP_4$ antibodies which target general epithelial markers found on numerous epithelial tumor and normal cells. Therefore, specific information on the primary tumor type is not available, hindering both therapeutic decision-making and understanding the micro metastatic process in individual tumor types.

3. The usual practice of manual IS performed after IE is not standardized, leading to increased variability in CTC detection between laboratories.

4. CK20 is an epithelial protein expressed in the normal epithelial cells of the colorectal tissue and that this profile is maintained in malignant cells. Therefore, CK20 immunostaining can be detected in both normal and malignant cells of the colorectal tissue.

5. The prognosis for CRC patients with distant metastasis, lymph node involvement and recurrence is very poor. Early detection of metastasis and relapse is essential to improve their survival. Approximately 40% of CRC patients, without evidence of metastatic disease, subsequently develop recurrent disease in 5 years. This shows that the current staging system alone is insufficient for accurate patient prognostication.

Elements critical to the solution of the problems:

We recently overcame the limitation of only detecting general epithelial cells using immunomagnetic beads coupled with anti-$BerEP_4$ antibodies by blocking detection of those antibodies so that anti-CK20 antibody can be used to demonstrate the gastrointestinal (GI) origin of the $BerEP_4$ positive cells in CRC patients (Figure 1). This advancement revolutionized immunomagnetic CTC detection by allowing the use of antibodies against tissue-specific markers so that an accurate diagnosis of the tumor type can be made. This is critical for therapeutic decision making and also enables us to understand the micrometastatic process for that particular tumor type. CK20 is a more specific marker than both CK and $BerEP_4$ to detect CRC in the blood because CK20 is expressed only in cells from the GI tract, urothelium and epidermal Merkel cells. This is in stark contrast to the much broader spectrum of expression for CK and $BerEP_4$. Therefore, CK20-positive CTCs may more accurately reflect the CRC patients' conditions.

Our team designed a standardized protocol composed of IE and IS using an automatic immunostainer and stringent criteria for morphological analysis. These measures would facilitate reproducible results in the staining process and their objective assessment, which are essential in standardization.

It is now recognized that the identification of occult micrometastatic disease in cancer patients would have important roles in the establishment of prognosis, treatment decisions and monitoring of the efficacy of adjuvant treatment. In the past, micrometastatic detection was mainly focused in the bone marrow. However, aspiration of bone marrow is time consuming and uncomfortable for the patient. Therefore, current research now concentrates on detection of tumor cells in the peripheral blood. Our preliminary results of an elevated number of CK20-positive CTCs in metastatic CRC patients but not in patients with benign colorectal diseases and normal subjects can demonstrate that CK20-positive CTCs may have prognostic significance in CRC patients.

Potential significance of the results:

The use of CK20-positive CTCs as a biomarker in detecting metastatic CRC not only facilitates a more specific diagnosis at the circulation level, but also provides a more accurate prognostic information to the clinicians. Identifying CRC patients who are at particularly high-risk of relapse and metastasis non-invasively so that appropriate adjuvant treatment strategies with intensive protocols can be applied to improve the chance of survival. Our breakthrough in successful blocking detection of the anti-$BerEP_4$ antibody linked to the magnetic beads has opened up a new era in CTCs detection because the tumor origin of CTCs can be detected using their respective specific antibodies. Therefore, in the long run, our work may assist clinicians to make a specific diagnosis, predict prognosis accurately and deliver an effective treatment to the patients with various types of CTCs.

Chapter 2

BREAKTHROUGH IN POINT-OF-CARE TESTING: DIAGNOSTICS FOR EVERYONE, ANYWHERE, ANYTIME

Ricky Y.T. Chiu, Felix Chao

Need for Novel Point-of-Care Testing Systems

Accurate and timely diagnostics are needed to prevent and protect the global population from constant threats. These include natural threats from disease epidemics, as well as man-made from irresponsible food safety or environmental pollution. Furthermore, the possibility of mass bioterrorism is an ever-growing possibility. Existing laboratory methods, such as cell culture, immunoassays and nucleic acid related tests, enable the accurate identification of pathogenic or chemical threats. However, the ability to combine speed, access and accuracy in an ideal device is a constant hurdle in the development of novel diagnostics. The closest combination of these features is generally found under the umbrella of point-of-care (POC) or in-field diagnostics. However, no technology exists today that enables a diagnostic system that fully satisfies all characteristics of the ideal device, especially for regions poor in resource.

There is a significant need to develop next generation POC diagnostics that can enable the constant monitoring of natural and man-made threats with appropriate accuracy and timeliness.

Advancements in laboratory-based testing over the years have enabled accurate and faster test results at a lower cost. Biotechnology companies, such as Hong Kong's Diagcor, are at the forefront of novel laboratory-based testing and diagnostic equipment. Their advanced flow-through hybridization instrument reduces the time of the common polymerase chain reaction (PCR) from hours to minutes, significantly decreasing time to result and associated testing expenses. Furthermore, they have expanded cost-effective diagnostic access to regions where laboratory testing services were previously unavailable.

However, advanced lab-based assays present inherent restrictions that confine their ability to solve all of today's diagnostic needs. Time to result can still take 1-2 days for clinical sites with nearby centralized laboratories and up to two weeks for remote areas due to the need to collect and transport samples[1]. More importantly, laboratory testing is still strictly limited to developed nations where there is an established laboratory infrastructure, capital equipment and highly skilled personnel.

POC testing, on the other hand, is defined as diagnostic tests that are performed at or near the site where the patient is located. Thus, these tests are performed in decentralized settings that typically do not have access to laboratory equipment or trained personnel. POC settings include physician's offices, urgent hospital departments (e.g., emergency room, intensive care), rural health clinics, student clinics, pharmacies, military locations and mobile testing units. POC testing systems are characteristically performed by non-laboratory personnel such as physicians, nurses, assistants in medical offices, emergency medical technicians (EMTs), and the patients themselves (self-testing). The lack of infrastructure and training at these sites creates strict requirements for allowable costs and complexities of POC diagnostics. Thus, these devices are typically based on inexpensive technologies such as dipsticks, assay strips or other manual tests with minimal complexity. Although complex portable instruments (e.g. desktop PCR or Polymerase Chain Reaction machines and readers) have been developed for POC settings (e.g., Cepheid's Gene Xpert and Alere's Alere I), the capital costs and requirement for additional training continue to make them impractical for most decentralized sites.

Advantages of POC Testing

POC testing provides several key advantages that are unavailable with centralized laboratory testing. Rapid results where the patient is being treated can be used for immediate medical decision making and patient management while the patient is still in the physician's office, clinic, or hospital. **Circumventing the time and steps needed to send samples to a central laboratory for testing results could mean the difference between life and death.** Further, enabling immediate consultation will allow for more streamlined and cost-effective healthcare. Physicians will not have to re-familiarize themselves with the patient case files prior to making clinical decisions and follow-up visits can be eliminated, saving time and costs for both the patient and the healthcare system.[2] The potential impact of this advantage becomes especially apparent with certain clinical scenarios such as the management of sexually transmitted infections (STIs), such as Chlamydia trachomatis (CT). Although, treatment for CT is relatively simple (one dose of azithromycin), the majority of cases are asymptomatic and require laboratory testing and follow-up visits prior to treatment.[3] Reliable POC testing would significantly improve the effectiveness of STI healthcare by enabling same-visit testing and treatment.

Another major advantage of POC testing is the ability to offer diagnostic services for under-served populations that might otherwise not have access to laboratory diagnostic testing due to location (rural or remote areas) or lack of healthcare resources. While the economically developed countries have access to medical equipment, trained personnel, and resources to perform diagnostic tests for the majority of diseases and conditions, these same resources are not accessible in many parts of the world. Unfortunately, it is in many of these same resource poor countries

where the need for rapid and accurate diagnosis of diseases is the greatest. These countries experience considerably higher disease-related deaths due to the lack of early diagnosis and the administering of timely treatment. As such, the World Health Organization has developed the ASSURED criteria as a benchmark for designing ideal diagnostic tools to best address the medical needs of Third World or resource-poor countries. The ideal diagnostic should be the following: Affordable, Sensitive, Specific, User-friendly, Rapid and robust, Equipment free, and Deliverable to end users.[4] A momentous example is the dramatic impact of rapid POC tests for malaria and other mosquito-borne diseases in sub-Saharan Africa. Although, there is still much room for improvement for existing malaria rapid tests, they have shown to be a valuable complement to existing detection methods and to expand the coverage of diagnosis.[5]

Overall, POC testing systems have the potential to save countless lives and improve patient outcomes, globally and across all demographics. Improved patient outcomes will lead to more streamlined and cost-effective healthcare systems at a time when health care costs are rising at historical rates.[6]

Disadvantages of Existing POC Tests

However great the potential is for POC tests, the use and proliferation of many POC diagnostic systems beyond current applications has been strictly and perpetually hindered by the devices' lack of sensitivity. That is to say, although many POC testing systems represent a significantly faster, more cost-effective and convenient diagnostic test than standard lab tests, the lack of sensitivity relative to lab-based tests confines the technologies' potential. When developing new POC testing technologies, there is typically a balance between access and accuracy to be considered. In many cases, a decrease in diagnostic accuracy may be acceptable if the diagnostic is able to provide an increase in access compared to existing testing methods. Novel POC diagnostic technologies are striving to eliminate the compromise by providing both high access and high sensitivity.

POC testing also comes with an increased potential for user error as the tests are performed in decentralized sites with minimal equipment and training. Locations performing POC testing have to work with a varying number of tests performed by personnel who might not be proficient with all diagnostic systems. Therefore, documentation of test results, operator identification, and internal controls can be challenging for POC settings.[2] Centralized laboratories have the advantage of having a connected network of equipment and electronic health records that make transmission of test results seamless. The lack of interconnectivity with laboratory and hospital information systems with many POC devices means that POC test results must be entered manually in order to capture and store in electronic health records. This can impede clinical processes, patient monitoring and drive up healthcare costs.

Finally, for cases where POC diagnostics are used for self-testing, the patient does not receive feedback or clinical input from a medical professional regarding the test result. This can be harmful for the patients as they may not understand the relevance or urgency of such test results unless they involve a clinician. Furthermore, self-testing without communication with a clinician creates a disconnect between the population and public health, leading to missed opportunities to measure epidemiological statistics or control potential epidemics. However, as POC testing technologies advance, so will its connectivity with wireless devices and the web. With 5 billion mobile subscribers, smartphones provide a promising digital platform for POC diagnostic systems. This technological trend will very quickly and significantly impact existing healthcare frameworks by advancing telehealth and revolutionizing the communication of test results.[7]

Paper-based POC Technology

Of all the POC diagnostic systems, the paper-based lateral flow immunoassay (LFA), is considered the most commercially successful based on its widespread applicability and utilization (glucose meter products rank the highest in terms of revenue generated). By 2010, over 100 companies worldwide were producing a range of LFA based tests with a total market valued at over 3.0 billion USD.[7]

The LFA diagnostic is operated by adding the sample to the proximal end of the strip (the sample pad). The sample migrates to the conjugate pad where antigens in the sample encounter and interact with immobilized particulate conjugates. The conjugates are typically a colloidal gold or latex particle to which either an antigen or antibody has been affixed (depending on the format of the assay). The sample rehydrates the conjugated particles and the analyte in the sample interacts with the conjugate, after which both migrate in complex to the nitrocellulose membrane. As the sample reaches the reaction portion of the nitrocellulose, it encounters a complementary component (either antibody or antigen) with which the conjugated particles can interact only via the presence of the analyte (the presence of which the assay is testing for). A positive result causes a buildup of conjugated particles at the test line, which is interpreted by either a presence or absence of a line, read by either the naked eye or a specialized reader. The entire operation requires no additional equipment, power supply or manual interaction other than the application of the sample to the sample pad.

For the past 30 years, the LFA diagnostic system has dominated the market of rapid diagnostic testing. The technology has been modified for a wide range applications including the well-known over the counter pregnancy test, such as the ClearBlue Digital (Geneva, Switzerland) and the First Response Early Result Pregnancy Tests (Ewing, NJ).[8] The diagnostic system has also been used to develop rapid POC tests for HIV (Orasure, Bethlehem, PA, USA), syphilis (Trinity Biotech Bray, Co Wicklow, Ireland), malaria (Alere, San Diego, CA, USA), drug of abuse and many others.

The technology's success can be attributed to the fact that it combines a variety of advantageous parameters, such as cost efficiency, portability, simplicity of use and speed, which are not altogether found in other diagnostic systems. These advantages are in large part due to the assay's utilization of paper (a mesh of porous fibers) as the construct for the bioassay. Paper is a readily accessible and inexpensive substrate, allowing for low cost of goods sold and higher profit margins. The material is inherently able to transport fluids via capillary flow. This allows paper-based diagnostics to eliminate the need for pumps and other external equipment to drive fluid flow and sample flow.[9] To this end, many research groups have considered utilizing paper as the material for designing next generation rapid POC diagnostics. In addition, because there is a long history of paper being used as a construct for bioassays, many techniques for paper functionalization have already been established and can be leveraged for product development. **Recently, there has been a push to further improve the performance of paper-based LFA diagnostic systems and to extend its capabilities to solve current day diagnostic needs.**

LFA diagnostic systems are typically utilized when a yes or no answer is required and that the target biomarker exists in the sample at high concentrations. The need for high concentrations of the biomarker is due to the fact that only a small volume of sample is allowed to flow past the antibody-based detection mechanism of LFAs. The small sample size creates a bottle neck for diagnostic sensitivity and signal. In the case of the widely accepted over-the-counter pregnancy test, the target biomarker, human chorionic gonadotropin, exists in urine in very high concentrations. However, for many infectious diseases, the limiting factor for detection is the low concentration of the pathogenic bacteria in the patient sample. Many groups have investigated the utilization of signal amplification, such as the incorporation of enzyme labels to enhance the signal read out. However, the increased signal achieved with this method is still not sufficient to enhance the LFA diagnostic system for many testing needs.[10] Thus, the limited sensitivity provided by the paper-based LFA system continues to hinder the diagnostic system's overall potential and applicability.

New Advancements in Paper-based POC

The major challenge for designing novel paper-based POC tests is to ensure sufficient sensitivity for the assay. As mentioned previously, target biomarkers for many diseases and conditions exist in concentrations too low for the conventional LFA to detect. Low sensitivity results in false negative test results, leading to the need for confirmatory laboratory testing in many cases. In order to combat the low concentration of the target biomarkers in the patient samples, potential strategies to improve the performance of conventional LFA diagnostics include signal amplification, electrochemical detection and concentration of the target biomarkers prior to detection. The difficulty in all of these strategies, however, is to maintain the low threshold for cost, complexity and training needed to meet the restrictions of decentralized clinical settings.

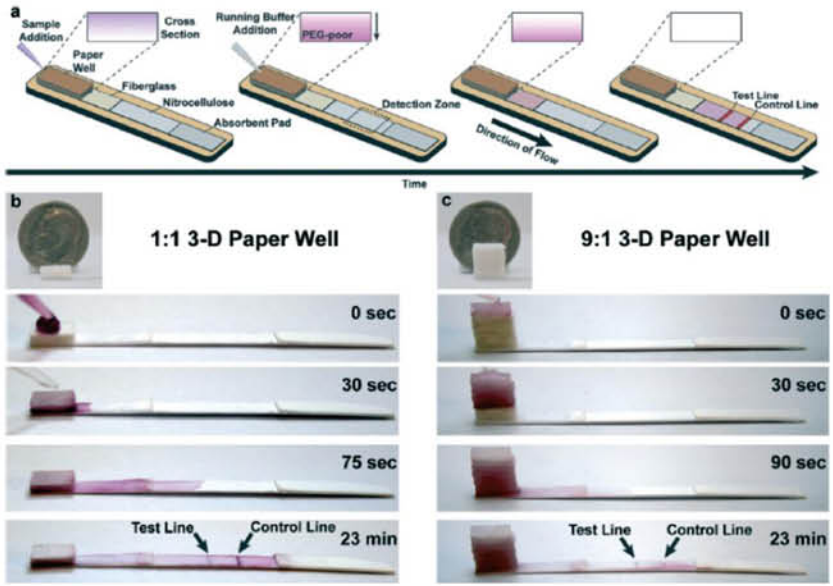

Figure 1. A 3-D paper well allows for ATPS separation while flowing through the well. (a) Analyte bound to gold nanoparticles is concentrated in the polymer-poor solution that flows through the paper and is able to react with the test or control line. (b) Separation in a 1 : 1 ATPS polymer : salt system and (c) 9 : 1 system with stacked paper sample well. Reproduced from Chiu, R. Y. T.; Jue, E.; Yip, A. T.; et al. Simultaneous Concentration and Detection of Biomarkers on Paper. Lab Chip 2014, 14, 3021–3028, with permission of The Royal Society of Chemistry.

The Kamei Group at the University of California, Los Angeles, tackled the problem of low sensitivity inherent to conventional LFA through the integration of an innovative concentration module.[11] The system utilizes upstream thermodynamic partitioning with aqueous two phase systems (ATPSs) to concentrate the sample prior to standard downstream LFA detection. The diagnostic system is constructed with a polymer-salt ATPS combined with a 3D fiberglass paper-based LFA to seamlessly concentrate and detect target biomarkers as the sample flows through the device. Advanced paper-microfluidics were used in the design of the novel diagnostic system to enable full functionality without the need for additional equipment, power supply or training. A schematic of the novel diagnostic system is shown in Figure 1.

In 2008, the Kamei Group was the first to utilize ATPSs to concentrate genomic DNA. The novel system utilized a micellar ATPS that consisted of phosphate-buffered saline (PBS) and a nonionic surfactant.[12] The scalable liquid-liquid extraction format of the ATPS made it unique for POC testing applications as it was compatible with low sample volumes. In addition, the utilization of a water-based concentration system, rather than a typical oil-water system, is that it enables a mild environment for the handling of target biomolecules. The first generation micellar ATPS concentration system existed in a homogeneous mixture until phase separation was induced by an increase in temperature. Micelle-poor and micelle-rich phases were formed with the target biomarker partitioning extremely to the micelle-poor phase due to experiencing greater repulsive, steric, excluded volume interactions with the larger and more abundant micelles in the micelle-rich phase. Thus, by varying the volume of the micelle-poor phase, the group demonstrated the system's ability to concentrate target biomarkers in a predictive fashion. For example, when a volume ratio of 1:9 was used, the micelle-poor phase became 1/10th of the initial volume, allowing for an approximate 10-fold concentration of the target biomarker.

In 2010, the Kamei Group, led by Dr. Ricky Chiu, became the first to utilize the ATPS concentration system in conjunction with LFA detection. The group was able to demonstrate a 10-fold concentration of bacteriophage M13 while utilizing the aforementioned micellar ATPS system.[13] Furthermore, by extracting the micelle-poor phase containing the concentrated target biomarker, they were able to demonstrate a 10-fold improvement in the detection limit of a conventional LFA detection system when compared with that obtained without ATPS concentration.[13]

However, one major drawback of the first generation micellar ATPS concentration system was that it took hours for complete phase separation at a 1:9 volume ratio (translating to a 10-fold concentration), making the system grossly impractical for rapid POC applications. To this end, the Kamei group investigated alternative ATPSs that could perform phase separation in a much faster timeline. The group therefore developed a polymer–salt ATPS system that achieved phase separation and concentration within 30 minutes for a 1:9 volume ratio system. Similar proof-of-concept data was generated with this novel system that demonstrated a 10-fold improvement in detection limit when the concentrated sample was run on a conventional LFA strip.[14]

Although the new polymer-salt ATPS significantly improved the time to result of the overall diagnostic system, further improvements were still needed to realize a viable POC diagnostic system. First, the 30 minutes for phase separation was still too long for a rapid diagnostic, resulting in a total time to result of approximately 45 minutes, longer than the standard patient visit (30 minutes). Further, the concentration system was not fully integrated into the LFA diagnostic mechanism. Manual extraction of the concentrated sample and application to the LFA strip was still needed, which would increase complexity and required training. In order to overcome both of these hurdles, the Kamei Group investigated integrating both the concentration and detection mechanisms into a single paper strip using advanced paper microfluidics. By designing a 3D paper well consisting of layers of stacked paper (see Figure 2), phase separation of the ATPS and concentration of the target biomarker was allowed to occur within the paper strip prior to downstream detection with the standard LFA mechanism. The novel paper-based system was able to increase the cross-sectional area normal to the fluid flow, which allowed greater sample volumes and improved the coalescing of microscopic domains for phase separation. In addition, the 3D design leveraged gravity to speed up the phase separation process.

The new diagnostic design demonstrated a dramatic increase in the efficiency of phase separation. The polymer-salt ATPS at 9:1 volume ratio was now observed to phase separate within 6.5 minutes on the paper strip, compared to approximately 2 hours in a test tube.[15] Furthermore, by integrating the concentration process with the detection mechanism, the new diagnostic design eliminates the need for manual extraction and application of the concentrated sample for LFA detection. These advancements enabled phase separation, concentration and detection to occur simultaneously and seamlessly within a single paper-based device.

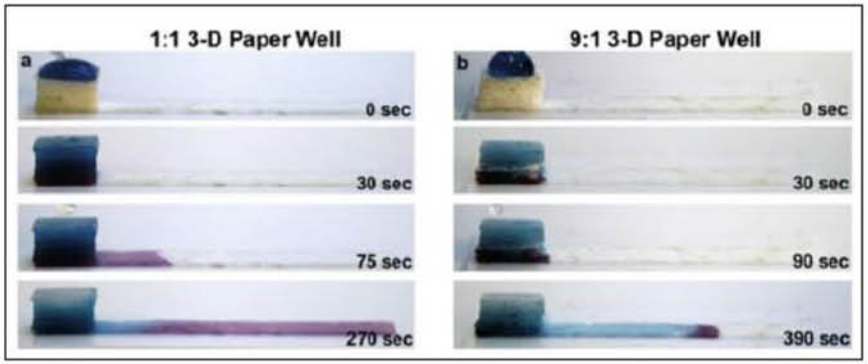

Figure 2. Phase separation using 3D paper wells with a (a) 1:1 polymer-salt aqueous two-phase system (ATPS) solution and (b) 9:1 polymer-salt ATPS solution. Reproduced from Chiu, R. Y. T.; Jue, E.; Yip, A. T.; et al. Simultaneous Concentration and Detection of Biomarkers on Paper. Lab Chip 2014, 14, 3021–3028, with

Dr. Chiu and the Kamei Group has since then licensed the technology from the University of California, Los Angeles to further commercialize the diagnostic platform. Dr. Chiu is the co-founder and CEO of Phase Diagnostics, an early stage biotechnology start-up company based in Garden Grove, California, USA. The company is funded by the National Institutes of Health, National Science Foundation and the Bill and Melinda Gates Foundation. Furthermore, they have raised a $1.7 million Seed round from a diverse group of Hong Kong investors, including the CEO of Diagcor, Dr. Joseph Tam. Phase Diagnostics has since then further developed the technology to minimize user interaction. The diagnostic system has been optimized to integrate all components of the ATPS within the paper device such that all that is needed to perform the test is the application of the patient sample. Thus, from the end-user's point-of-view, there is no difference between the next generation system and the conventional LFA in terms of usability and speed of results.

Phase Diagnostics is leveraging their novel diagnostic platform to develop rapid, inexpensive and easy to use POC tests for major unmet and global testing needs. These products have the potential to provide novel testing solutions that will revolutionize healthcare for sexually transmitted infections, operations for food safety and the eradication of malaria in sub-Saharan Africa. See Figure 3 below for a schematic of the proposed final product for sexually transmitted infections, specifically Chlamydia trachomatis infection.

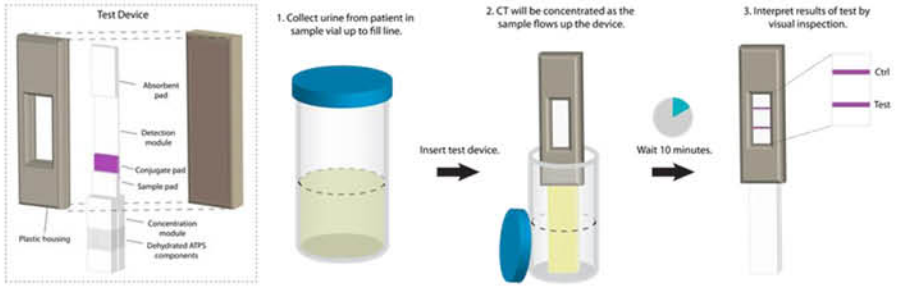

Figure 3. Schematic of our final product. The fully integrated ATPS and LFA test strip concentrates the CT bacteria found in urine, allowing for rapid and accurate diagnosis within 10 minutes with minimal user interaction.

Sexually Transmitted Infections

Chlamydia (Chlamydia trachomatis, CT) and gonorrhea (Neisseria gonorrhea, NG) comprise the leading group of treatable infections in the world. In South East Asia, there were an estimated 7.2 million new cases of CT and 25.4 million new cases of NG in 2008. In Western Pacific, including China, there were an estimated 40.2 million new cases of CT and 42.0 million new cases of NG in 2008.[17] Chlamydia and gonorrhea are known as "silent" diseases as most patients have no symptoms, and therefore remain largely undetected and do not receive treatment. The development of rapid POC tests for CT and NG with high sensitivity would prove extremely beneficial in improving diagnosis and treatment rates.

Phase Diagnostics is leveraging their technology to develop next generation rapid POC diagnostics for CT/NG infection that combines the ease-of-use and very low cost of rapid paper-based POC diagnostics with the very high accuracy of lab-based tests, enabling unprecedented reliability at the POC and at home. Availability of such a device will eliminate existing hurdles to CT/NG testing, replace lab-based assays and significantly expand testing accessibility to previously unreachable settings and populations.

Untreated CT/NG, symptomatic or not, may cause pelvic inflammatory disease, long-term pregnancy complications, even infertility. In addition, CT/NG increases the risk of comorbidities such as HIV and several types of cancer. Antibiotics are often

administered prematurely due to the long time to result of standard lab assays and the possibility of patients not returning for treatment. This aggressive use of antibiotics has led to the development of multi-drug resistant strains, especially for gonorrhea, which has been labeled as one of the top 3 urgent bacterial threats by the CDC.[18] Many antibiotics are no longer effective against gonorrhea, and if this trend continues, the remaining options may only be the most severe antibiotics that are reserved only for serious hospital-based infections.

In many parts of the world, the access to laboratory-based testing is extremely limited, either by the lack of centralized laboratories or the inability of the patient to afford such services. **The limited testing access results in the incapacity to identify the majority of positive cases as more than 70% of all CT/NG cases are asymptomatic.**[17] This results in unknown transmission and re-transmission between partners and the inability to control the CT/NG epidemic. Furthermore, traditional lab-based CT/NG assays prevent the ability to test-and-treat within one patient visit due to their long turnaround times (approximately 48 hours). This delay results in an additional group of positive cases that do not receive treatment due to the patients not returning for follow-up treatment.

Existing rapid and inexpensive POC diagnostics, such as Quidel's QuickVue and Alere's Clearview lateral-flow immunoassay test strips are grossly inadequate with sensitivities less than 50%.[19] Newer generations of rapid PCR machines such as Cepheid's Gene X-pert, prove to be highly accurate; however, the capital expense severely limits their access. See Table 1 below for comparison of existing solutions.

Table 1. Comparison and evaluation of existing clinical testing methods for CT/NG

Test	Fixed costs	Per test price	Time to result	Sen-sitivity	Training	Response
Traditional lab*	$0	>$100	>2 days	>95%	None	Established method of testing; however, no same visit test-and-treat capability
Existing LFA	$0	~$20	~20 min	<50%	Moderate complexity	Allows same visit testing, however, grossly inadequate accuracy
Portable PCR	~$20k-$50k	>$50	~2 hr	>95%	Moderate complexity	Cost and training requirements make it impractical for most decentralized testing sites; time to result still too long for same visit test-and-treat
Next Gen LFA	**$0**	**$15**	**10 min**	**>95%**	**None**	**Combines advantages of all testing methods, enables both clinic and consumer use**

***Fixed costs and training are relative to the clinical end user that sends in samples for testing and billed by the reference laboratory.**

Phase Diagnostics' technology has the potential to enable next generation LFA diagnostics for CT/NG that can significantly increase access to testing. An accurate paper-based device for CT/NG will eliminate the need for laboratory equipment and training. Limited testing access is a major driver for many of the current obstacles obstructing the control of STIs. Reliable POC testing will decrease the need for clinicians to diagnose and treat presumptively as well as provide a viable means for enabling routine screening to identify asymptomatic cases. Furthermore, the inability to provide same visit testing and treatment is a major shortcoming of current STI healthcare. The need for a follow-up visit prior to treatment results in continued patient transmission in the interim as well as missed opportunities to treat positive patients who do not return for follow up. **The ability to provide instantaneous results will allow for timely and accurate treatment, reducing overall CT/NG incidence and increasing antibiotic stewardship.**

For the general population, Phase Diagnostics' technology has the potential to enable the first over-the-counter (OTC) product to complete a multi-panel CT/NG test. From the patients' point-of-view, embarrassment is the major pain point of STI testing. The

need for confidentiality drives these patients to utilize family planning centers and STD clinics for testing. However, these settings are not always ideal. Patients often experience long wait times at the clinic and difficulties in making appointments. In addition, the major concern heard from young patients was the long turnaround time for results, or in some cases, complete lack of notification for negative cases. This created extremely stressful experiences. In addition, healthcare providers will be able to send such devices home to be used for test-of-cure after treatment to confirm the patient has been cleared of infections. Treated patients can also screen their partners to determine if the infection has spread, reducing the possibility of retransmission. **Enabling private home testing will eliminate the embarrassment inherent to STI testing, leading to an increase in screening rates and identification and treatment of asymptomatic cases.**

There is a desperate need to break the cycle of disease transmission to decrease overall CT/NG burden in the community. Physicians and public health leaders are advocating for the development of novel rapid POC tests for CT/NG that can disrupt the current healthcare framework for STIs and enable proper disease control.

Food Safety

The global food industry – including farms and agricultural production sites; distributors; food processors; retail; import and export customs; and food service industry – relies on product testing programs leveraging in vitro diagnostics or IVD products to ensure food safety. **Phase Diagnostics is aiming to disrupt the food safety testing industry by providing faster and more cost-effective in-field diagnostics for microbiological pathogens and common toxins.**

Food safety is threatened by microbial pathogens (primarily bacteria), viruses, natural (commonly microbial) toxins, other environmental toxins (direct or indirect industrial contamination), food allergens, genetically modified organism (GMO) content, food adulterants, inauthentic food products, agricultural chemicals (pesticides, herbicides, fungicides), and others.[20]

Acute illness and fatality from the limited consumption of a food is commonly a result of the food's contamination with bacterial pathogens. Food safety diagnostics are used foremost for the detection or identification and quantification of bacterial pathogens, most commonly Salmonella, Shiga toxin-producing E. coli (STEC), Listeria, and Campylobacter. Most cases of acute illness, hospitalization and fatality from the limited consumption of a food are associated with bacterial pathogens. In addition, natural toxins are proven to be potential carcinogens and also capable of causing damage to the hepatic, endocrine, neurological, respiratory, cardiovascular, and gastrointestinal systems.[20]

The growing size of China's food production and consumption makes China's food supply and food safety issues of major interest to global markets and partners (namely, Hong Kong). A major source of foodborne disease in China stems from the shortage of clean water and poor sanitation. In addition, chemical pollution is a major threat to both agricultural land and freshwater supplies. The rapid development of industrial facilities in rural areas, often immediately adjacent to agricultural land, is an escalating food safety problem because fields are being contaminated by industrial wastes, such as heavy metals. Finally, in the context of agricultural production itself, overuse and misuse of certain agrochemicals pose another set of major concerns for public health and food safety as fertilizer overuse is widely acknowledged in China.[21]

There is a significant need for rapid and inexpensive diagnostics to increase surveillance of food safety risk in light of global changes in regulations and food supply.

Global food safety requirements are becoming more and more stringent. As "testing prior to release" is likely to become more prevalent in industries abroad as a fail-safe against outbreaks, usage of "24 hour" tests and other rapid molecular tests with shorter times to results will be integral for successful operations. Furthermore, risk-based Hazard Analysis and Critical Control Point (HACCP) systems (a management system in which food safety is addressed through the analysis and control of biological, chemical, and physical hazards from raw material production, procurement and handling, to manufacturing, distribution and consumption of the finished product) are becoming the standard for most manufacturing and distribution sites. The changing food safety requirements along with existing and ineffective testing methods results in the inability to test and release food product (especially perishables) in a timely manner and to achieve sufficient and robust testing in order to catch all cases of contamination.

Culture-based traditional microbiology is the "gold standard" for food safety pathogen testing with the highest volume of usage in pathogen testing. Culture-based laboratory testing is also commonly used for confirming results from rapid in-field testing. See below Table 2 for comparison of testing methods. However, culture-based microbiological tests are limited to only pathogen detection and take days for results. Immunoassays are more versatile in application, however, require long enrichment and

incubation steps to be successful in detecting low concentrations of pathogens. These delays with microbiological and immunoassays create costly logistical issues when perishable products are waiting to be cleared at customs or released. Existing rapid tests (e.g., lateral-flow immunoassay (LFA) and agglutination tests) are only accurate enough for the screening of pathogens and still require a confirmatory laboratory test due to their poor limit of detection. Finally, molecular diagnostics (e.g., PCR), while fast and accurate, are too expensive to conduct wide spread testing of all products, resulting in lower sampling and the risk of contaminated products reaching the public.

Table 2. Comparison and evaluation of existing food safety testing methods

Testing Methodology	Accuracy	Speed	Cost	Versatility	Response
Microbio (e.g., culture)	High	> 5 days	Low	Low	limited to only pathogen detection, long time to result, resulting in costly logistical issues
Immuno (e.g., ELISA)	High	> 3 days	Med	High	Long time to result, resulting in costly logistical issues
Molecular (e.g., PCR)	High	~ 1 day	High	Med	Too expensive to conduct high volume / high throughput screening
Rapid tests (e.g., LFA)	Low	~ 2 days	Low	High	Poor sensitivity, still requires a confirmatory laboratory test
Next Generation LFA	High	~1 day	Low	High	**Combines advantages of all testing methods, significantly decreasing time to result**

The ability of our technology to seamlessly and rapidly enrich the target biomarker will significantly reduce the enrichment steps required by existing immunoassays (e.g., ELISA), significantly reducing the time to result. Reducing the timeline needed for product food safety testing has the potential to streamline supply chain operations and reduce costs.

For countries that rely heavily on imported food, such as Hong Kong, timely customs inspections are critical to streamlined logistics and delivery. Inspectors of the Hong Kong Centre for Food Safety (CFS) take samples at import, wholesale and retail levels for microbiological, chemical and radiation testing. Microbiological testing covers both bacteria and viruses, while chemical testing includes natural toxins, food additives and contaminants. The CFS promotes public awareness and surveillance results for public dissemination. Hong Kong has been moving towards international testing trends, focusing on risk assessment and target surveillance of specific microbiological pathogens. Rapid tests to screen for high risk pathogens will be ideal for import settings to uphold existing food safety processes as well as adopt new international standards.[22]

Furthermore, the U.S. Department of Agriculture's (USDA's) Food Safety and Inspection Service (FSIS) has widened obligatory "test and hold" procedures among meat processors and ready-to-eat (RTE) food processors in order to mitigate pathogen-related recalls.[23] Although traditional microbiology and testing with enrichment steps may still be used for "test and hold" procedures, the hold time favors expedited testing and rapid testing methods. Therefore, there is a strong need and market for novel diagnostics that can provide rapid and accurate results at an affordable cost to ensure robust and complete testing.

Malaria

There were an estimated 207 million cases of malaria infection and 627,000 associated deaths due to the disease in 2012. The majority of those infected were young children and pregnant women. Of the deaths, approximately 90% occurred in sub-Sahara Africa due in large part to the lack of accessible testing resources.[24] There is a critical need for earlier detection of the disease in order to enhance diagnosis, enable faster administration of treatments, and improve outbreak prevention. These regions are in dire need for POC assays that enable accurate, rapid, equipment-free, easy to interpret and low-cost testing.[25]

Successful malaria elimination initiatives will necessitate highly effective and inexpensive diagnostics to identify infected patients, including those which are asymptomatic with low parasitic burden. Rapid POC diagnostics have been essential in the fight to control malaria, but currently lack the requisite sensitivity to facilitate elimination. Furthermore, screening uptake by existing rapid tests have been limited due to the risks and difficulties involved with finger-prick blood collection, including potential biohazard exposure and blood taboos. The next generation of malaria rapid tests must have the ability to detect low density infections and be favorable for mass population screening in resource poor settings and in low-incidence regions.

Furthermore, conventional LFA for the detection of Plasmodium falciparum lactate dehydrogenase (pLDH), an enzyme produced by the malaria-causing parasite P.falciparum, was shown to accurately diagnose malaria in only 78% of patient whole-saliva samples. In order to ensure more accurate results in saliva samples, the sensitivity of LFA must be improved, while maintaining its ease-of-use.

To address this need, Phase Diagnostics has initiated the development of a saliva-based rapid test for malaria that is fully integrated and does not require equipment, power or trained technicians. Our technology, will enable paper diagnostic devices that are highly sensitive, avoid the need for blood collection and remain very inexpensive to implement. Phase Diagnostics is currently funded by the Bill and Melinda Gates foundation to collaboratively tackle the existing malaria epidemic in sub-Sahara Africa.

Wireless Capabilities

"Telehealth" is the use of medical information exchanged from one site to another via electronic communications to improve a patient's health status. The field includes a growing variety of applications and services using two-way video, email, smart phones, wireless diagnostics and other forms of telecommunications technology. It can also encompass health care that uses telecommunications technologies such as videoconferencing, transmission of still images and diagnostic results. This is a rapidly growing segment of the overall healthcare industry. The market for wireless technologies in healthcare was valued at $4.4 billion in 2010 compared to $1.7 billion in 2005.[7]

Early POC devices conducted tests and reported the results to the patient or healthcare provider, asynchronously in most cases, but did not interface with other devices, and also did not communicate with the hospital or laboratory information systems. The lack of wireless capabilities meant that results from these tests were either entered manually, or this data never became part of the patient's electronic medical records. However, timely communication and retention of test results is critical for effective healthcare.

Current smartphones provide a promising digital platform for mobile POC diagnostics, as they are equipped with a high resolution camera, a powerful processor with high storage capacity, wireless connectivity, real-time geo-tagging, secure data management, and cloud computing. With more than 5 billion subscriptions worldwide, the cellphone, as a ubiquitous platform, can be utilized for imaging, sensing, processing and communicating health-related data in field settings using already embedded digital components.7 Therefore, this existing wireless telecommunication infrastructure provides the framework to incorporate an arsenal of Telehealth functions.

Expanding upon the example of STI screening, an over-the-counter test for CT/NG with Telehealth capabilities (e.g., companion mobile phone application) will allow the patient to test in the privacy of their own homes, eliminating the embarrassment and social stigma heavily associated with STI testing. Furthermore, by leveraging the processing power of mobile phones, the test can be designed to be more sensitive, while at the same time, decreasing the possibility of potential user error. Finally, the mobile application can facilitate the communication of results to a primary care physician who can provide consultation and to schedule a follow-up appointment for treatment. If a primary care physician is not available, personalized healthcare resources can be provided at the very least such as a list of STI treatment options (e.g., nearby STD clinics and family planning centers). All of these data can be provided to local public health departments to better monitor and provide population based healthcare.

As communication and mobile technologies become more advanced and accessible, novel diagnostic technologies must evolve with Telehealth capabilities in mind to fully leverage the potential of POC testing. The shift towards consumerism and personalized healthcare will drive the need for more effective applications to diagnose, measure and monitor patients' health. Furthermore, the combination of the aging world population as well as the desire for instant information from younger generations will give rise to a significant demand for home diagnostic capabilities without the need for a physician's visit.

Point of Care and Precision Medicine

The National Institutes of Health (NIH) defines precision medicine as "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person." The approach enables clinicians to provide personalized treatment and prevention strategies for individuals or groups of people. Compared to the "one-size-fits-all" approach, where clinical recommendations are developed for the average person, precision medicine has the potential to allow for a significant improvement in patient outcomes.

In 2015, former US President Obama announced the launch of the Precision Medicine Initiative — a bold new research effort to revolutionize how we improve health and treat disease with approximately $215 million USD in funding.[26] One year later, China initiated its own national plan for precision medicine, enlisting the efforts of academic, public and private sectors. Funding has been speculated to approach upwards of $9.2 billion USD.[27] Near term goals for precision medicine are focusing on cancers as they are among the leading causes of death worldwide. In addition, recent research has already established that each cancer has its own genomic signature and tumor-specific

features allowing for risk assessment, diagnostic categories, and therapeutic strategies, with increasing use of drugs and antibodies designed to counter the influence of specific molecular drivers.[26] Longer-term precision medicine has the potential to generate knowledge applicable to the whole range of health and disease by collecting molecular, genomic, cellular, clinical, behavioral, physiological, and environmental parameters. The ability to collect these data, however, will rely on the development of novel diagnostics that enable more accuracy, access and connectivity.

As the global precision medicine initiative generates more data on genomic, physiological, environmental and social risk factors for diseases and conditions, the ability of POC diagnostics to provide disease data for real-time analyses makes them critical for preventative and precision medicine. Novel POC technologies and diagnostics have the potential to screen, alert and monitor high-risk patients and provide for meaningful clinical intervention. These personalized recommendations can therefore improve patient management, treatment and overall patient outcomes (Figure 4).

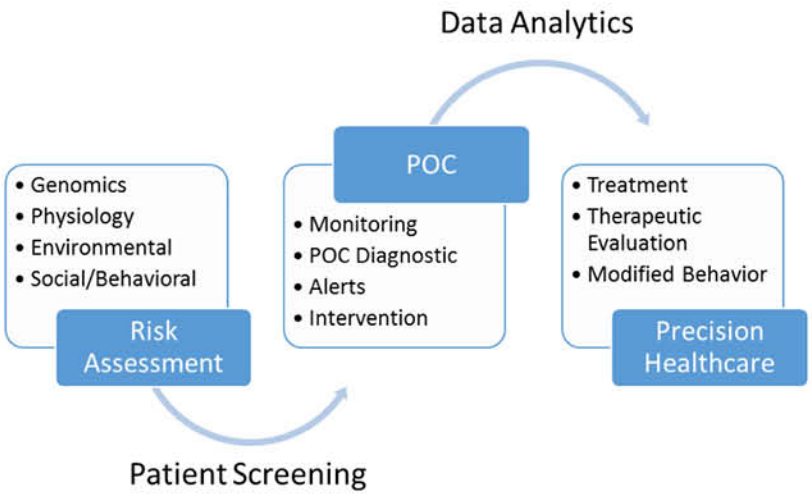

Figure 4. Flow chart towards the implementation of precision healthcare. Reproduced from Dhawan, Atam P. "Collaborative Paradigm of Preventive, Personalized, and Precision Medicine With Point-of-Care Technologies." IEEE Journal of Translational Engineering in Health and Medicine 4 (2016): 1-8.

As a current example, NIH funding for POC tests for sexually transmitted diseases has been targeting the development of urine and swab-based tests that can be performed in the privacy of the patients' own homes. The goal is to achieve home-based tests that are as accurate as laboratory testing and can upload data to healthcare providers and electronic heath records to collect valuable disease parameters for further precision medicine efforts.[28] Currently, POC tests are being developed for chlamydia, gonorrhea, trichomonas, syphilis, herpes simplex virus (HSV), and HIV. As mentioned previously, these POC tests have the potential to provide same visit testing and treatment (with no loss to follow-up), decreased transmission of the disease, and potential for immediate counseling. Combining these capabilities with wearable sensors with connectivity can provide effective screening and monitoring of high-risk patients at homes and decentralized settings.

Impact on Asia Pacific Healthcare

China and Asian Pacific countries represent clear examples of resource-poor regions and developing territories where there is a need for technologies that can expand healthcare access. It will be some time before these countries are able to establish a healthcare infrastructure (i.e., capital equipment, highly trained professionals, and access to central hospitals) comparable to developed countries that can offer affordable and accessible disease testing and monitoring for the majority of the population. Therefore, during the interim, there is a strong need for diagnostic technologies that can provide basic services without the need for existing capital equipment, technical knowledge and training. The new polymer-salt ATPS technology is best suited for these countries as the growing healthcare system would be able to heavily leverage two of our technology's key strengths: low cost and ease-of-use.

As the fastest growing biotechnology industry in Asia, Hong Kong is an ideal hub to establish and provide healthcare services to these regions. Hong Kong can be considered the door way to China under the "one country, two systems" policy whereby Hong Kong has access to China's technical staff, research findings and enormous market. A partnership with Hong Kong will significantly increase the potential for success for a US-based company. Therefore, Phase Diagnostics is partnering with DiagCor, one of Hong Kong's leading biotechnology and diagnostic innovators to combine efforts in delivering expanded testing access to both China and Asian Pacific countries. Collaborations between US and Hong Kong companies will spur the establishment of a biotechnology hub. In addition, the strong push by the Hong Kong government to nurture the biotechnology industry makes this an ideal time for exciting collaborations to accelerate the development of the biotechnology sector.[16]

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Chapter 3

INTERNATIONAL COLLABORATION IN MEDICAL DEVICE INDUSTRY

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Abstract

Benefit of collaboration across border

Medical and healthcare devices are developed by engineers (hardware/software) according to the hypothesis or belief of the cause, detection and therapy of disease and disorder postulated by pathological scientist and clinical therapist, who subsequently perform statistical proof of efficacy of the engineered device.

In advanced US or EU countries, expensive and sophisticated equipments support pathological scientific research to prove out various concepts for disease development and therapy efficacy. In Asia, especially China, plenty of intensive researchers and engineers support device iterative optimization, re-prototyping, process facility set-up, equipment customization and installation, mass production automation for quality and cost, and customization for local market. Huge numbers of patient cases also support various trial tests. In Hong Kong, the business environment encourages legal, finance, fund raising, initial design integrating multi-disciplines, initial prototyping for functional test, IP protection application, and wide angle innovation of alternative comparative design solutions. Collaboration across borders has comparative advantage.

Medical Device Joint Ventures in China

"In 2014, the import and export value of medical devices in China was approximately USD 35.7 billion, a 4% year on year increase. China's medical device total import value was USD 15.7 billion, a 5% increase from 2013. Joint Venture (JV) and Wholly Foreign-Owned Enterprise (WFOE) were the main importers of medical devices, making up almost 40% of China's total import value of medical devices in 2014. Importers of medical devices were mainly from private companies; JVs (52%), WFOEs (39%), and State Owned Enterprises (SOE) (9%) of China's medical device import value (see Fig. 1). Major importers include Johnson & Johnson Medical Companies[1], Medtronic[2], Shanghai Dong Song International Trading Co Ltd[3] and Olympus Trade (Shanghai) Cr Ltd[4].

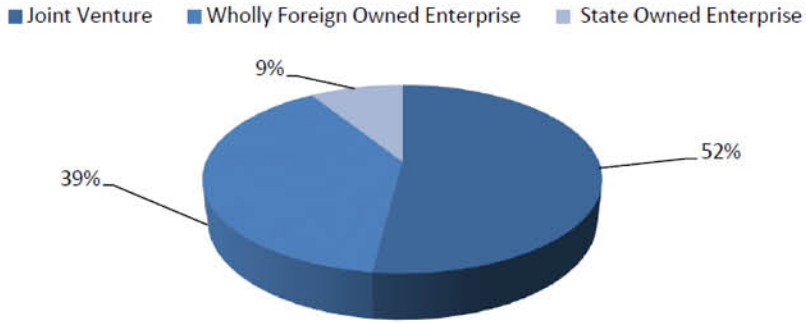

Fig.1 – Major Import Company Type in China, 2014

China's medical device industry is concentrated in eastern and southern coastal regions. Many foreign companies have established manufacturing bases in the Yangtze River Delta (Shanghai and Jiangsu province) and Bohai Rim (Beijing and Tianjin). In terms of medical device products, the Yangtze River Delta has a cluster of companies

1. http://www.jjmc.com.cn/.
2. http://www.medtronic.com/.
3. http://www.dongsong-cn.com/.
4. http://www.olympus-global.com/en/corc/grouplist/index.jsp?r=5746.

that produce disposable syringes and infusion sets. Computerized Tomography (CT) machines are mainly manufactured in Beijing by companies such as GE. Philips established a JV with Neusoft Medical System, Philips Neusoft Medical Equipment System in 2014. This JV mainly manufactures CT, MRI, X-Ray and ultrasonic machines.[5] In 2013, it was announced that Neusoft and would purchase 25% of Philips equity in the JV.[6] Shenzhen has become an important city for high-end medical devices over the last decade, with rapid developments of devices in medical imaging, blood analyzers, and patient monitors."[7]

According to the report compiled in partnership with the EU SME Centre and China-Britain Business Council describing the medical device market in China, the Chinese government has issued a number of preferential policies to improve the share of domestically made Chinese medical devices in the market. The term "domestically made" does not refer to products that are manufactured in China exclusively, but also products whose raw materials were sourced from China and JV products where the higher proportion of shares is owned by Chinese investor(s). Funding schemes were set up by the Chinese government to improve the R&D capabilities of Chinese medical device manufacturers, approve channels for innovative medical device registration, give priority to Chinese branded medical devices during hospital budding processes, and legislate that public hospitals should prioritize domestic brands by providing a recommended list of domestic medical device suppliers for this purpose. These measures help to stimulate the demand for domestically made medical devices, and also increase the quality of domestically made medical devices over the past few years as many JV invested a lot in R&D and they are standing out with high quality products meeting best international standards in some important global medical trade shows like China International Medical Equipment Fair (CMEF) in China or MEDICA in Dusseldorf, etc.

5. http://www.jobcn.com/cozone/38/20/382007/page.
6. http://www.neusoft.com/news/html/20130705/2474143227.html.
7. Sector Report – The Medical Devices Market in China, compiled in Partnership with EU SME Centre and China-Britain Business Council.

Industry Features in Hong Kong

According to the report conducted by Hong Kong Trade Development Council (HKTDC) in March 20171, Hong Kong medical and healthcare equipment industry has two distinct markets: the household consumer and professional or institutional (hospitals and clinics). Most Hong Kong medical and healthcare equipment companies are engaged in original equipment manufacturer (OEM) business, such as producing massagers and blood pressure monitors for household consumer use; and rubber molding, plastics/resins for institutional use. With increased competitiveness in price and product development, the Chinese mainland is increasingly putting pressure on Hong Kong local companies, inducing them to strive for product and company repositioning. Many Hong Kong-based companies also provide engineering design services in order to enhance their competitive edge.

To lower production costs, many Hong Kong manufacturers have relocated their production facilities to the Chinese mainland. However, quality control, marketing, research and development, design, as well as material and equipment procurement continue to be conducted in Hong Kong.

Many of Hong Kong's medical and healthcare goods are exported under OEM arrangements with supplied product specifications and designs. Hong Kong manufacturers are highly regarded for their handling of customers' intellectual property (IP) and sensitive technology. In recent years, Hong Kong manufacturers have become increasingly involved in product design and development, engineering, modeling, tooling and quality control. In order to differentiate themselves from low-end products, many Hong Kong manufacturers apply for different international certifications for their products.

8 http://hong-kong-economy-research.hktdc.com/business-news/article/Hong-Kong-Industry-Profiles/Medical-Healthcare-Equipment-Industry-in-Hong-Kong/hkip/en/1/1X-000000/1X00409R.htm

Apart from producing for OEM customers, some Hong Kong manufacturers also have in-house R&D departments to develop models produced under their own brand names. For these original brand products, Hong Kong manufacturers would sell to overseas importers and distributors, who would also act as agents to provide an after-sales services. It is advised that manufacturers/distributors take out insurance or make other arrangements to minimize the risk of product liability claims.

Obstacles in West-East Industry Collaboration

Foreign companies often face a problem of poor understanding of the Chinese health system and regulations. As many companies tend to formulate their business strategies in China according to their previous experiences in other countries, this regularly results in over-estimation or under-estimation of sales figures and a poor market entry experience.

The Chinese medical device market is "stamped" with Chinese characteristics, such as government regulations, intricate market rules, and cultural nuances. As such, many strategies that work in Europe or the US do not succeed in China. Moreover, many firms underestimate the time required for investment in China. They believe that they are likely to see high profits within three to five years. However, it takes a lot of preparation to be able to take advantage of Chinese opportunities successfully, and a significant period of time is needed to establish lucrative working partnerships. It is very important to seek a reliable local partner who can assist companies entering China to navigate through the local business environment. A good local partner should have well-established industrial connections and good relationship with market insiders and the China Food and Drug Administration (CFDA).

There are some other reasons that may lead to the failure of the collaboration. Some foreign companies are lacking a strong distribution network, in which the product(s) can be easily overtaken by competitors with well-established distribution network and their me-too but cheaper version of product(s) with minor improvements. The product portfolio is too narrow (some of the partnership may only focus in one single product) so that the company is lacking in related product(s) to synergize on the same distribution network and consumer advertising. Lack of trading business is also a problem as it will be difficult for the company to maintain vital revenue flow with distribution network and good brand image for customized product before selectively developing some self-invested products with proprietary innovation.

Forming complementary partnership with non-duplicated expertise

Besides the previous traditional role split of using Hong Kong/China as manufacturing service provider, more foreign companies are exploring the opportunity to set up co-owned strategic alliance or JV to further use Hong Kong/China in redesign for market customization (particularly to suit local market). Below, the table shows the comparative strength of different complementary partners (see Fig. 2).

Strength	Partners from
Scientific research and proof of concept	Advanced US or EU countries
Industrial design for ergonomics and user preference	Hong Kong
Functional design integrating multi-technologies and crude prototyping	Hong Kong or China
Optimized design (for use, manufacturing and 3P) and re-prototyping	China
Tooling, pilot production	China
IOPQ validation	Hong Kong supervise execution in China
Clinical trial protocol/ execution/ conclusion	Hong Kong/ China/ Hong Kong
510K release / pre-market approval	Regulatory authority in countries of sales to consumer
Test market launch with pre-sale and post-sale support and surveillance	Countries of sales to consumer

Fig. 2 - Comparative strength of different complementary partners

Below graph shows the evolving forms of partnership in medical device industry (see Fig. 3). Partners from potential OBM master manufacturer, product marketer and risk investor (Role Split C) should have several years of experience from global giant medical device companies in order to learn professional skills in market research, clinical study, competitor benchmarking, product planning, writing business plan to raise capital, global exhibition, logistics, advertising, establishing sales network and post sales support and surveillance. Role Split C company can be fabless and outsource the work to the external experimental design firm (Role Split D) for design service and

OEM factory (Role Split E) for contract manufacturing service, but they should be responsible for buying or licensing the intellectual property (IP) right of the product(s) as they are the product owner.

Role Split D company can carry out technical research, experimental design and prototyping. They can also refine the design for use and initial manufacturing, providing project management and technology support to OEM contract manufacturer. Role Split E company can modify the design by Role Split D company to suit for mass manufacturing. They optimize the total cycle excellence and perform re-prototyping if needed. They repeatedly perform the tooling and manufacturing services until the final pilot production (PP) units are completed. Once the PP units are ready, they will be passed to animal trial and clinical research centre (Role Split F) for clinical research to support regulatory application. Once the engineering sample units are ready, they will be passed to Role Split F company for animal trial.

The product and market specialists from country-exclusive importer (Role Split B) can perform the local market research and study the country regulation related to the product. The product generalists from district wholesaler and retailers are responsible for the sales and customer relationship management.

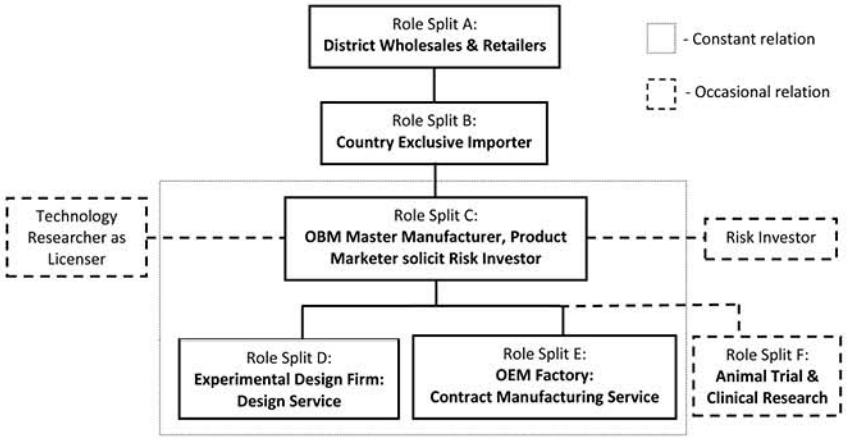

Fig. 3 - Evolving forms of partnership in medical device industry

Stages in commercialization cycle

Commercializing a medical device is not easy. The commercialization path is rarely the same for different devices, as there are so many nuances that are based on the classification of the device, country of origin, manufacturing process, etc., which can make the process difficult to navigate, but the general stages of the commercialization cycle can be summarized as follows.

Stage 1: University applied research for partial prototype as proof of concept in advanced US and EU countries because of government sponsorship.

Stage 2: Design realization converts partial proof of concept into complete product design for usability test and user preference including size and weight because of mutli-technology integration speed and IP integrity of Hong Kong professionals, and economy of China professionals.

Stage 3: Carry out design improvement for reliability, small-scale manufacturing economy and total cost of ownership under collaboration of Hong Kong and China professionals.

Stage 4: Design and fabricate manufacturing equipment and tooling; make and submit off-tool pilot production lot to regulatory approval; and then launch in test market because Hong Kong has plentiful experience in setting up manufacturing, control quality in China factory and continuous improvement and innovation of China professionals.

Stage 5: If test market result convinces ten-fold potential, redesign to optimize product and manufacturing facility for large-scale manufacturing to expand market and product development and variety customization because Hong Kong has well understanding of Asian market needs and customization, while China has experience in economical mass production and quick logistics.

9. Chapter 26 – A bridge from the West to Chinese manufacturing in Business Insights: China – Practical Advice on Entry Strategy and Engagement

Our West-East Collaboration examples

Design House Collaboration: SGAI

In 2002, Sagentia, one of the world's pre-eminent technology management and product development companies, was managing new product development and Chinese-based manufacture for seasoned western major branded customers. As the project progressed, it was clear that a growing percentage of Sagentia's consultancy costs were being inefficiently spent on cultural mismatches and so Sagentia made the decision to open an office in Hong Kong, setting up the office SGAI – a joint venture between Sagentia and AML, a leading Hong Kong-based electronic products manufacturing company.

During the years of collaboration, SGAI was awarded several medical device projects from different clients, e.g. electronic pipette, electronic incontinence curing products, laboratory stem cell rocker and shaker systems, etc. AML, as a local partner, provided the cultural know-how and day-to-day management of the projects, allowing both parties to focus on their core competencies and making sure the business was done in cost and time effective way.

Quality control is essential for medical device projects. Forward-thinking Chinese companies, such as AML, already recognized the benefits improved quality control can bring, and have exploited Sagentia's expertise in quality assurance (QA) processes and procedures to improve the quality of design, development and manufacturing processes throughout, thereby providing further reassurance for clients in the West.

SGAI was an excellent example showing the mutual benefit of everyone involved in the east-west JV business. SGAI was profitable within eight months of opening its doors and it helped the country meet the target of moving up the value chain, so it was the reason why SGAI won the Cathay Pacific Award for "Innovation and Dynamism" in 2006.[9]

University Collaboration: Stem Cell Bioreactor

In 2006, a professor from one of the most renowned UK universities approached AML to co-develop a stem cell bioreactor. This product was designed for 3D bio-processing, and to provide a better platform for fast production of stronger stem cells than the traditional stem cell culture. It is designed with a gas permeable membrane for the required protection and developed to meet the essential requirement such as repeatability, reproducibility and controllability. In the development and manufacturing of the device, it has applied up-to-date electronic technologies, e.g. system on chip, feedback control for accuracy and stability. With as short as 6 months lead time, this collaboration completed the entire process of product development for commercialization, from design with excellence, prototyping, tooling, testing and manufacturing. This project has defeated 37 competitors, won the Machinery and Tools Design Grand Award from the Hong Kong Awards for Industries in 2008.

Impact Investment Collaboration: Surgical Robot

In 2014, AML started to participate in the development and fabrication of a top UK university-led surgical robot project funded by impact investments. Such surgical robots are complex, intelligent, lightweight and natural to use with seamless user control. They can enhance the current surgical workflow, rather than alter it radically or become a hindrance to normal procedures. This project is still undergoing, and the collaboration is working towards the development of next generation of miniaturized and intelligent mechatronic devices and robots for flexible access surgery, as well as investigating new techniques for providing synergistic control between the surgeon and the robot.

Startup Collaboration: Electronic Food Allergy Tester

In 2016, a US start-up company approached AML to co-develop a food allergy testing device. This product contains a discreet and portable sensor that can detect gluten in liquid and solid foods in about two minutes. The sensor combines an electronic sensor with antibody-based detection in a disposable capsule. This process turns a completed eight-step laboratory food testing process into an easy three steps. The collaboration is still continuing and an updated version of the device with expanded sensors is expected to come to market in late 2017.

Other suggestions and recommendations

In maximizing the success rate of the partnership, government should invest in entrepreneurship training courses, form complementary partnership network with proactive scanning and pairing service, and introduce angel mentor to coach complementary partnership, orchestrate a realistic business plan and venture governance to reduce the failure rate and venture capitalist to fund expansion beyond breakeven scale. Government should also provide training and a co-investment loan (repayable after profitable for tax) to support the early stage of entrepreneurship after training and co-investment of the accredited angel mentor.

Startup enterprises can consult angel mentor in realistic business planning and raise

funds through crowd prepayment for future production not yet tool-up. After off-tool pilot production, startup enterprises can raise expansion capital from VC or listing in new OTC capital market.

Chapter 4

AN ANALYSIS OF EVOLUTIONARY CONSERVATION BASED ON GENOMIC ORTHOLOGY AND PROTEIN-PROTEIN INTERACTION NETWORKS

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Abstract

Network modeling is one of the most popular and powerful tools for studying complex systems because it enables the thorough investigation of the multiple types of complex systems, both on local and global level. In this study, we employed GEDEVO, a network alignment dynamic algorithm, to measure the similarities of the PPI networks between different organisms. The coming comparative analysis of the evolution conservation between orthologous molecule level and PPI network revealed that the biomolecules are more conservative than molecular interactions in evolution. Our results offer insights of molecular basis and mechanisms for evolutionary studies.

Keywords:
Protein-Protein Interaction Networks, Evolutionary Conservation, Orthologs

Introduction

The recently emerged state-of-art approaches in the systems biology enables researchers to investigate biomedical sciences in terms of systems scale and level[1,2]. Amongst the many approaches, the approach of network modeling and analysis is one of the most powerful tools. It has been favored early on by a great number of scientists and thus quickly adopted as the gold-standard methodology in many of their research projects. One of the important reasons accounting for the high popularity of network modeling is that, it is of high compatibility and fitness for modeling a wide range of data. In other words, networks have advantages in visualizing and studying a variety of complex bio-molecular interactions. For example, the drug-target interaction data can be modelled into drug-target interaction networks, so as the protein-protein interaction (PPI) data, ligand-receptor interaction data and other kinds of data[3-6]. Now, we are embracing a series of novel and interdisciplinary research subfields coined with fashionable terms, e.g., network medicine, network pharmacology and network biology[7-9].

Revealing the evolutionary relations amongst organisms for reconstruction of the phylogenetic tree is always one of the key and central missions in evolutionary biology. To this end, many efforts have been made by scientists. Conventionally, researchers used to profile the evolutionary relation through a series of sequence analyses on biomolecules. For example, through sequence alignment, detection of the sequence similarities, or comparisons of regulatory elements and interaction/binding domains of the biomolecules[10,11].

Here in this work, we used the network alignment method to measure the similarity of PPI networks, so as to provide evolutionary insights. This network-based method enjoys two points of advantages. Firstly, as described previously, network models allow the global scope and thorough investigations of the whole bio-system, which integrates more data and comprehensively involves more factors than merely focusing on one or several biomolecules. Secondly, the network model consists of several biomolecules as the nodes and several interaction relation links as the edges. Rather than studying only one or several biomolecules without considering their complex relationships with their neighbor molecules, taking the subnetwork as the basic unit for evolutionary studies surely enjoys more advantages. For example, the subnetwork, as a unit in itself, usually represents or reflects a complete functional module in the biological network and hence is able to provide more structure-function relation, functional and evolutionary insights than methods of single biomolecule study.

In this study, we employed the GEDEVO, a network alignment-based dynamic algorithm, so as to measure the similarity, i.e., the subnetwork shared by two protein-protein interaction (PPI) networks from different organisms, so as to explore the evolutionary insights amongst these organisms.

Materials and methods

From BioGRID database, the curated PPI data of Drosophila melanogaster, Saccharomyces cerevisiae and Schizosaccharomyces pomb were collected (as of December 2016) and cleaned[12]. Upon collection and cleaning of interaction data from BioGRID, data were manually re-organized and then visualized in Cytoscape[13]. Then networks were subsequently submitted to the CytoGEDEVO[14] for alignment.

CytoGEDEVO is the implementation of the GEDEVO algorithm. Briefly, GEDEVO stands for the "Graph Edit Distance (GED) EVOlution". GED is the number of steps for transforming a graph into another one (Figure 1)

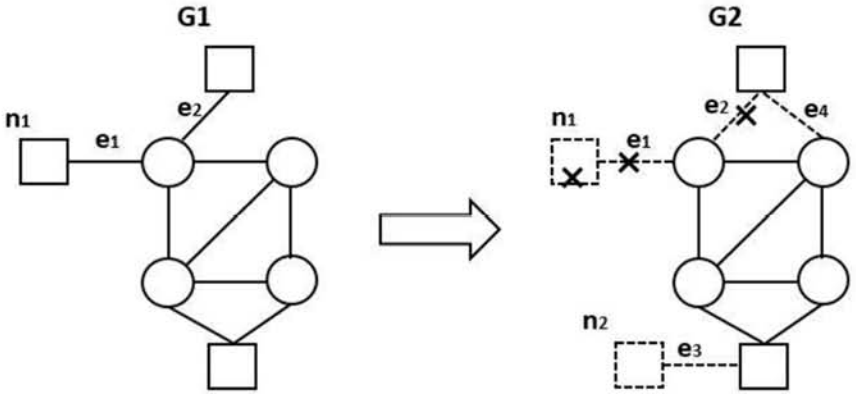

Figure 1. Graph Edit Distance (GED). Transforming graph G1 (Left) into G2 (Right): The edge e1, node n1 and edge e2 are deleted, while edge e4, node n2 and edge e3 are inserted. To count the deletion /insertion of edges/nodes as 1 unit of GED, and substitution of nodes/edges as 0, hence the total GED (G1, G2) is 6.

Upon determination of GED, Edge Correctness (EC) is computed. EC is a percentage with full value of 100%, and it is defined as $EC = (|E1| + |E2| - GED)/(2 \cdot \min(|E1|, |E2|)) \times 100\ \%$, where E1 and E2 are the edge sets of two networks aligned. If the EC is 100%, one of the input network is isomorphic to the other. EC algorithm detects the sub-graph differences easily and therefore is a good indicator for the similarity of two networks aligned.

Ortholog clusters between organisms were retrieved and counted from the Inparanoid database15. Data were normalized, statistically processed and subsequently integrated with the resultant data from network alignment for comparative analysis in the plotted charts.

Results

As seen in Table 1 below, we queried 3 typical organisms against the BioGRID database, and the bio-interaction data were retrieved from the database. Both physical interaction data and genetic interaction data were counted and listed.

Table 1. The list of 3 typical model organisms' bio-interaction data (As of December 2016).

Organisms	Physical interactions	Genetic interactions	Total interactions
Drosophila melanogaster	38642	9979	48621
Sacchromyces cerevisiae	135500	539710	675210
Schizosacchromyces pombe	12661	57844	70505

For the alignment analysis of the PPI networks, EC is used to indicate the similarity between two networks of the different organisms. The results are shown in Table 2.

Table 2. Results of the network alignment.

Organisms	*S. pombe*	*S.cerevisiae*	*D. melanogaster*
S.pombe	100%	23.28%	18.52%
S.cerevisiae	23.28%	100%	15.29%
D.melanogaster	18.52%	15.29%	100%

Both the results of network alignment and the count of the ortholog clusters were shown in charts of Figure 2 (a-c), in which each chart indicates the comparison between certain one of the organisms and the other 2 types of organisms. For instance, Figure 2 (a) stands for the comparison between S.cerevisiae and the other 2 types of model organisms. The light gray bars indicate the network alignment-based similarities between the PPI network of S.cerevisiae and the PPI networks of other organisms. The dark gray bars indicate the frequencies of ortholog clussters between S.cerevisiae genome and others' genomes, which reflects the percentages of the genes coming from the same ancestor gene.

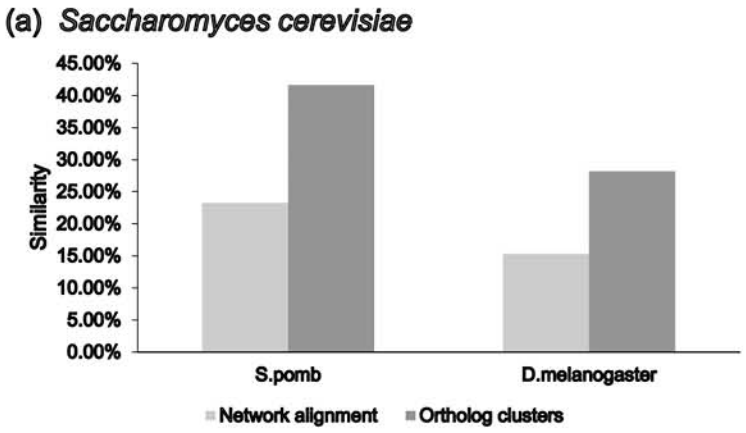

Figure 2 (a). The comparison of the similarities of PPI network and genomic orthologous between clusters S.cerevisiae and other model organisms. Light gray bars indicate the similarities of S.cerevisiae PPI network to others' PPI networks. The dark gray bars indicate the percentage of orthologous clusters shared by S.cerevisiae genome and others' genomes.

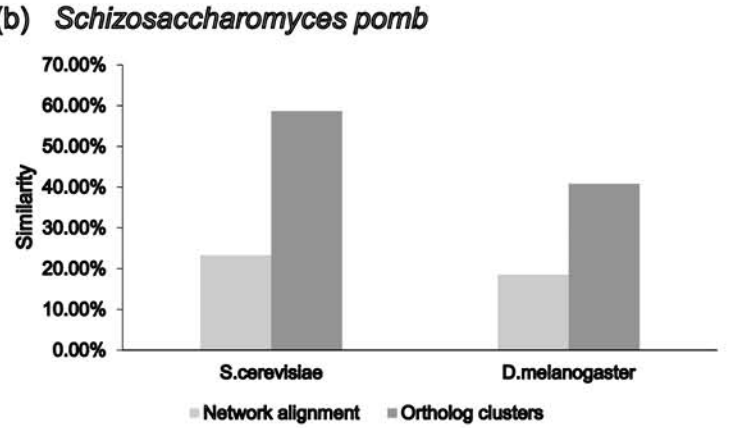

Figure 2 (b). The comparison of the similarities of PPI network and genomic orthologous clusters between S.pomb and other model organisms. Light gray bars indicate the similarities of S.pomb PPI network to others' PPI networks. The dark gray bars indicate the percentage of ortholog clusters shared by S.pomb genome and others' genomes.

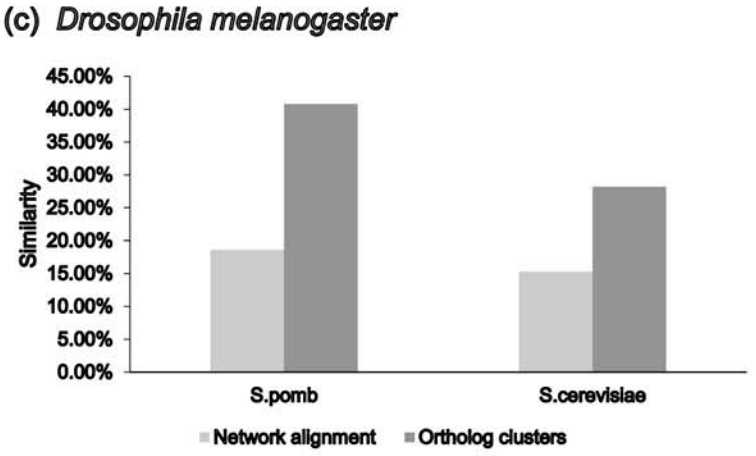

Figure 2 (c). The comparison of the similarities of PPI network and genome orthologous clusters between D.melanogaster and other model organisms. Light gray bars indicate the similarities of D.melanogaster PPI network to others' PPI networks. The dark gray bars indicate the percentage of ortholog clusters shared by D.melanogaster genome and others' genomes.

Obviously, all of the dark gray bars are higher than light ones in all charts. Our direct comparative analyses revealed that, phylogenetically, biomolecules might have slower process in varying and evolving, and hence they are more conservative than the interactions between biomolecules.

Discussion

Based on the approach of network alignment, we measured the similarities of PPI networks of different organisms. Through comparative analyses of the PPI network similarities, which reflect the evolutionary conservation on molecular interaction/functional, and the genomic orthologous clusters across different organisms, we found the higher degree of evolutionary conservation on molecular level than the molecular interaction level.

Further investigation and studies are required for elucidating the detailed reasons and complex mechanisms behind our discovery; though, one of the possible explanations is the intrinsically disordered protein (IDPs). IDPs is a family of proteins with dynamic and flexible structure. In more detail, with the full or partially flexible 3D structure, an IDP can switch its 3D structural conformation and promiscuously bind to different molecules, i.e., the interaction between an IDP and its interaction partners could be quite unstable and changeable. If the proteome of an organism contains a high number of IDPs, certainly, the protein molecules themselves would be more conservative than their interactions are. Unfortunately, current experimental techniques of biophysics still have difficulty in determining both the 3D structure and the total number of IDPs within the full proteome scale, which prevent our further investigating the relationships between IDPs and biological evolution.

Limitations exist and our work has space for improvement. First, the PPI data source are far from complete due to various reasons. This will surely result in incomplete PPI network of organisms, which will further affect the results of network alignment. Currently, full genome data of many organisms become freely accessible thanks to the next generation or high-through sequencing technologies. This is especially the case for frequently studied organisms, or so-called model organisms, such as yeasts, mice, and fruit flies. What is more, the genome data of the model organisms keep being re-sequenced in a relatively high frequency. In other words, multiple latest versions of the up-to-date genomes of the model organisms are available. Nonetheless, it is less lucky for researchers who are eager for the full proteome or complete PPI data. The reasons are complicated. Briefly, it is due to the dynamic features and temporal changes of the real-time and transient protein expression, which are beyond the detection ability of current technologies. Therefore, in order to obtain the full and complete data, more advanced technologies are required to be developed for the detection of proteome and PPIs. In one word, the inaccessibility of full PPI data makes for the less satisfying results of network alignment. Alternatively, in the future we may try to collect PPI data

from multiple sources, e.g., deposited experimental PPI datasets and results of text mining, so as to try best to construct the full and sound PPI networks for alignment analysis.

Second limitation is that we applied only one alignment algorithm in this work, which is insufficient for maximizing the results of our work. In the future, we plan to test and benchmark different network alignment algorithms, e.g., the IsoRankN16, so as to select the best one for problem solution. If there is no suitable solution, we will also consider further developing own specific algorithms for addressing specific issues.

Perspectives

In this work, we employed network analysis and comparative analysis to explore the phylogenetic relations, which is significant in revealing the insights in evolutionary biology. Our work is interdisciplinary and falls into the category of bioinformatics or computational biology, which is now an important subfield for biotechnology.

As a novel and interdisciplinary research field, the bioinformatics is developing rapidly in the research community of Hong Kong, too. For instance, Wang et al., developed new method to reconstruct the phylogenetic network17, and Lei creatively applied Bayesian Ying-Yang harmony learning, a semi-supervised approach, to address various challenges in biological networks18.

Nowadays, almost all industries including biotechnology are facing the revolution brought by high volume and overwhelming "big data". To deal with the challenges, the key point is the IT (Information Technology) because IT plays the fundamental role for digitalization and smartization of industries, such as financial, telecommunication and e-commerce. In biotechnology, the more industry-specific terms for IT is bioinformatics.

The good news is that, bioinformatics is still in its infancy. We look forward to the further prosperity in bioinformatics and biotechnology in Hong Kong.

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Chapter 5

DERIVED FROM NATURE, MODIFIED BY SCIENCE

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Abstract

Saponins are natural glycosides that occur widely in plant species and exhibit a wide range of biological properties. Despite tremendous efforts, previous attempts to use saponins as therapeutic agents have been hampered by their narrow therapeutic window and highly unpredictable haemolytic and other cytotoxic activities. By modifying its side groups, we discovered we could not only enhance a saponin's potency, solubility and activity, but could also eliminate its haemolytic activity without loss of biological activity. Using this approach, we have generated over a hundred thousand new saponins. In this report, we show that some of these new saponins we generated have great therapeutic potentials against cancers of the ovary, lung, pancreas, breast, liver, bladder, prostate, skin, bone, brain, blood cells, colon, cervix, skin, testicle, spleen, kidney, lymph, stomach and thyroid.

Introduction

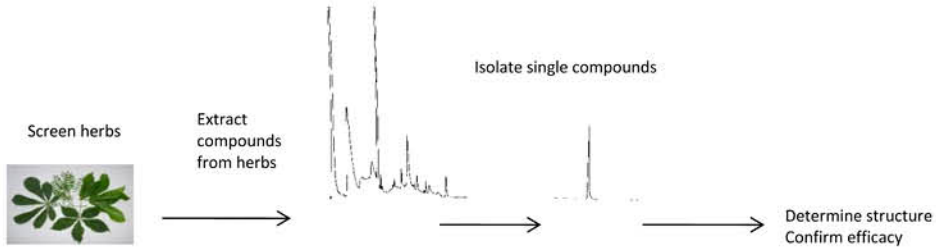
Saponins are plant glycosides with a core aglycone, which is either a steroid or a triterpene, to which subgroups are attached. The steroidal aglycone contains 27 carbon atoms, while the triterpenoidal aglycone contains 30 carbon atoms. The attached subgroups can be sugar moieties, hydrogen, hydroxyl, methyl, or acyl groups.

Saponins have been used throughout history as medication all around the world. They have been shown to have anti-cancer, hemolytic, antimicrobial, antifungal, and antiviral activities (Hostettmann and Marston,1995). Despite being used relatively widely, the mechanisms through which saponins produce their pharmacological effects is still largely unknown. In addition to the complexity of the functional groups, the structure-function relationships of saponins is further complicated by the fact that multiple functional groups may contribute to a specific biological effect.

Here we describe a method of producing a large number of saponins with a variety of functional groups that share the same target core. This allows their activities to be compared under the same conditions to give reliable data on each compound's activities. We further demonstrate that some of the newly generated saponins exhibit great medicinal potential against various types of cancer.

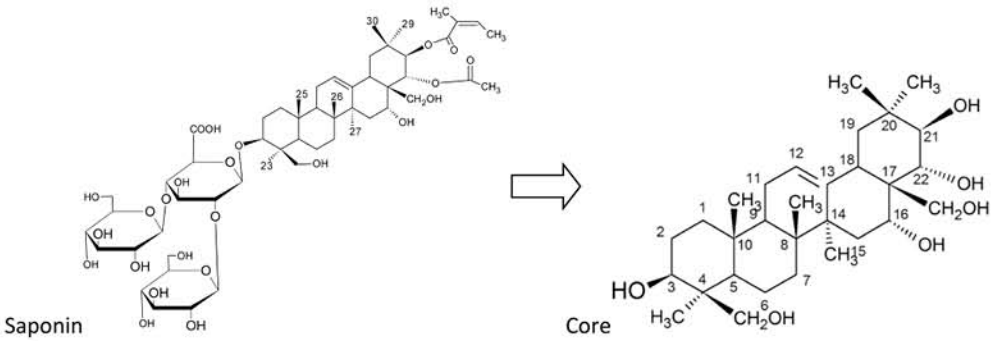
Method in saponins isolation from plants

We have established a platform to isolate saponins from plants:



Preparation of the saponin corefroma cytotoxic compound

We used β-Escin, a triterpene saponins, as the starting raw material in our studies. The saponin core was isolated by removing the side groups of the triterpene core with alkaline hydrolysis and acid hydrolysis.



Synthesis of novel active compounds

We attached functional groups to the core compound by esterification with an acyl halide. The esterification was carried out with various duration and temperature. The reaction was stopped with 5 ml of 2N HCl or 1M NaHCO3. The acylated products were then extracted 3 times with 10 ml of ethyl acetate followed by lyophilization under vacuum at 45°C. The reaction products were then dissolved in 80% acetonitrile, 0.005% Trifluoro acetic acid. The active esterification products were separated by HPLC/high performance liquid chromatography (45-100% AN/TFA for 80 minutes followed by 100%AN/TFA for an additional 110 minutes). Multiple fractions or compounds were identified and subsequently isolated again by HPLC. The concentration of the isolated compounds was dependent on the length and/or the temperature of the reaction. The activities of the acylated products were tested by the MTT Cell Proliferation Assay. The results showed that these compounds have different biological activities.

Below are the results of esterification of core compounds with tigloyl chloride, active compounds identification and their properties. The activity was determined by MTT cytotoxic assay.

Isolation of active saponins

Figure 1 shows the HPLC profile of esterification products of triterpene core compounds using tigloyl chloride. There are 8 main peaks with various small peaks of fractions.

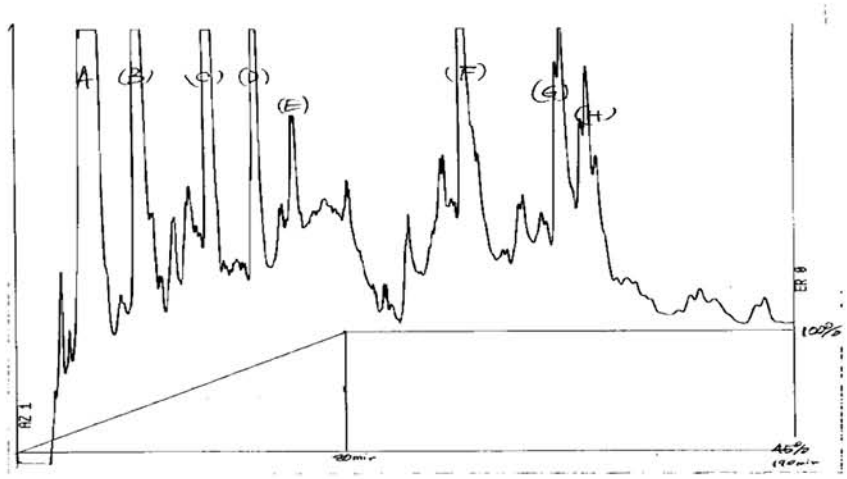


Figure 1

IndividualHPLC fractions were tested in the MTT assay for their cytotoxic activity against the following cancer cell lines: bone (U2OS), lung (H460), bladder(HTB-9), ovary (ES2), colon (HCT116), pancreas (Capan), ovary(OVCAR3), prostate (DU145), skin (SK-Mel-5), mouth (KB), kidney (A498), breast (MCF-7), liver (HepG2), brain (T98G), leukemia (K562) and cervix (HeLa). Active compounds were subsequently isolated from fractions with strong cytotoxic effects and were selected for further studies.

Potent cytotoxic effect of Saponin Drug-105 in selective cancer cell lines

One of the key features of an ideal cancer drug is the ability to target cancer cells specifically with minimal toxicity to other cells in the body. We have thus modified and selected compounds in line with this principle. Figure 2 below shows the IC50of Saponin Drug-105 in different cancer cell lines. The results show that Saponin Drug-105 has a very potent cytotoxic effect against ovarian and pancreatic cancer cell lines (2ug/ml and 2.5ug/ml) but is relatively non-toxic to other cells, thus demonstrating that our synthesis and isolation methodology could also be used to generate a large number of novel saponins with strong cytotoxic activity to specific cancers.

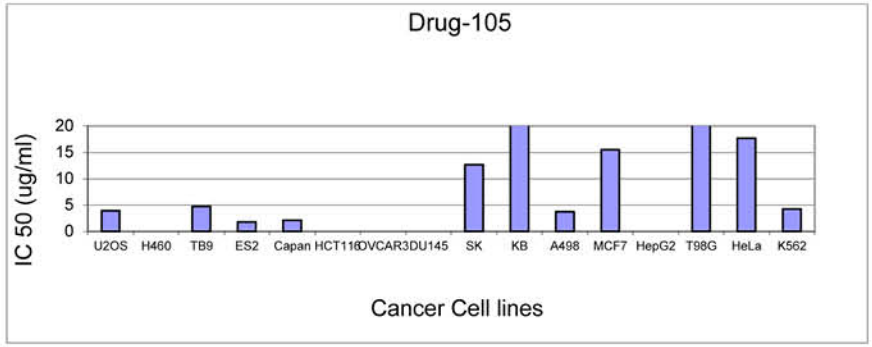


Figure 2

In fact, the number of saponins obtained can be further amplified tremendously by using different acyl-halides to generate different esterification compounds derived from one or more of multiple hydroxyl groups on a triterpene core. Obtaining such large numbers of compounds gives us the best chance of finding the most specific anti-cancer compounds.

The modified saponins that can be obtained with our methods is shown below Figure 3:

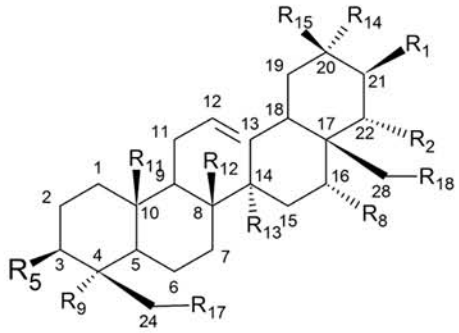


Figure 3

Where R1, R2, R3, R4, R5, R8, R9, R10, R11, R12, R13, R14, R15, R16 are independently selected from the group of hydrogen, hydroxyl, methyl,O-angeloyl, O-tigloyl, O-senecioyl, O-acetyl,O-Crotonoyl,O-3,3-Dimethylacryloyl, O-Cinnamoyl, O-Pentenoyl, O-Hexanoyl, O-benzoyl, O-Ethylbutyryl, O-alkyl, O-dibenzoyl, O-benzoyl, O-alkanoyl, O-alkenoyl, O-benzoyl alkyl substituted O-alkanoyl, O-alkanoyl substituted phenyl, O-alkenoyl substituted phenyl, O-aryl, O-acyl, O-heterocylic, O-heteroraryl, O-alkenylcarbonyl, O-ethanoyl, O-propanoyl, O-propenoyl, O-butanoyl, O-butenoyl, O-pentanoyl, O-hexenoyl, O-heptanoyl, O-heptenoyl, O-octanoyl, O-octenoyl, O-nonanoyl, O-nonenoyl, O-decanoyl, O-decenoyl, O-propionyl, O-2-propenoyl, O-2-butenoyl, O-Isobutyryl, O-2-methylpropanoyl, O-2-ethylbutyryl, O-ethylbutanoyl, O-2-ethylbutanoyl, O-butyryl, O- (E)-2,3-Dimethylacryloyl, O-(E)-2-Methylcrotonoyl, O-3-cis-Methyl-methacryloyl, O-3-Methyl-2-butenoyl, O-3-Methylcrotonoyl, O-4-Pentenoyl, O-(2E)-2-pentenoyl, O-Caproyl, O-5-Hexenoyl, O-Capryloyl,O-Lauroyl, O-Dodecanoyl, O-Myristoyl, O-Tetradecanoyl, O-Oleoyl, O-C(2-18) Acyl.

The following are examples of how our compounds can be used in the treatment of cancer.

Structural modifications greatly enhance growth inhibition

The NIH/NCI 60 cell-lines screening program further verified the difference in anti-cancer activity between the natural and our modified saponins. As shown in figure 4a, the potency of a natural saponinin inhibiting different types of leukemia was variable. In contrast, the potency of the modified saponin Drug-101was far more consistent in inhibiting different types of leukemia, as shown in figure 4b.

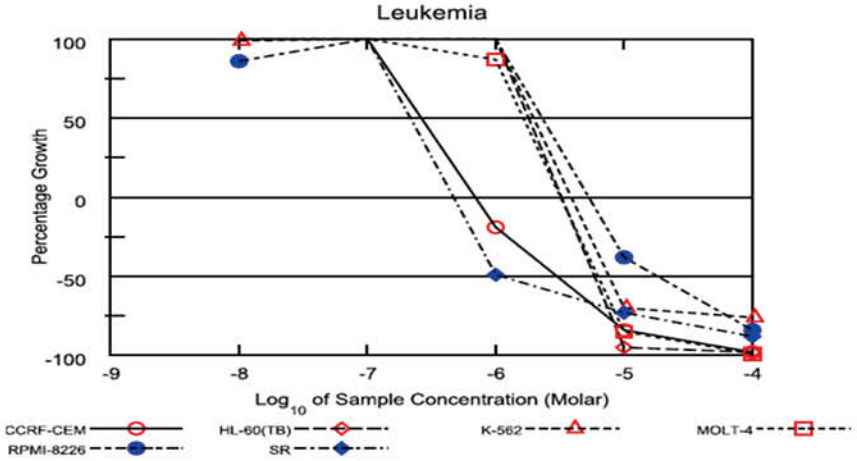


Figure 4a

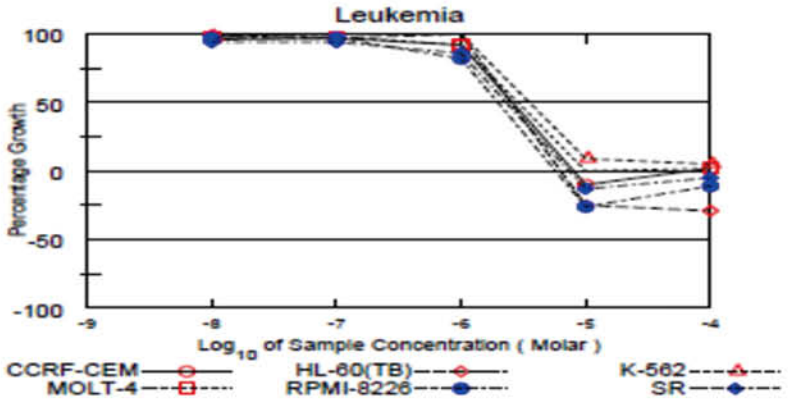


Figure 4b

Modified Saponins selectively inhibit cancer cell growth

A safe anti-cancer drug must have efficacy with minimal toxicity. Our modified Saponin Drug-102 has been shown to inhibit cancer cells more effectively than non-cancer cells. As shown in Figure 5 below, Drug-102 inhibited the growth of 90% of ES2 cancer cells, but only 45% of the normal human lung fibroblast WI38 cells in the same conditions, suggesting that Saponin Drug-102 has the potential to be developed into a safe anti-cancer drug.

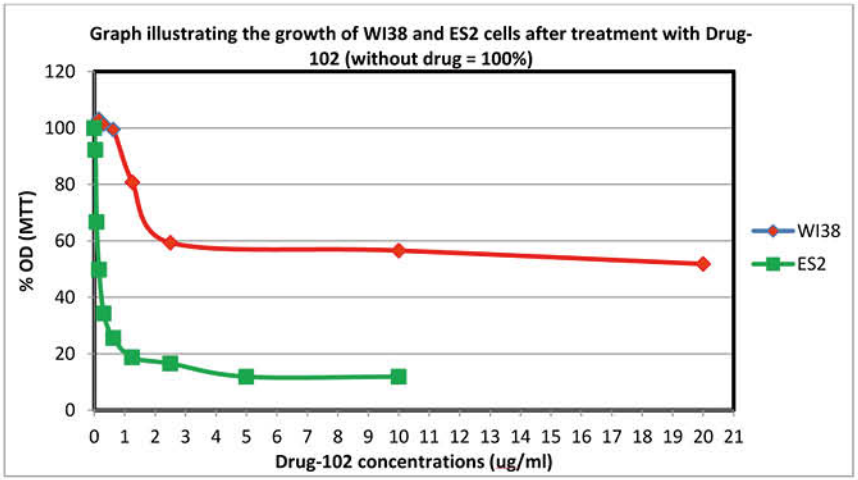


Figure 5

Modified Saponins are effective at inhibiting cell growth without killing cells (i.e., they are cytostatic)

An anti-cancer drug is much safer if its toxicity does not increase with increasing doses. Figure 6 below shows that modified SaponinDrug-102 inhibited the growth of Capan cells, which are derived from human pancreas carcinoma, with an IC50 value of about 2.2ug/ml.

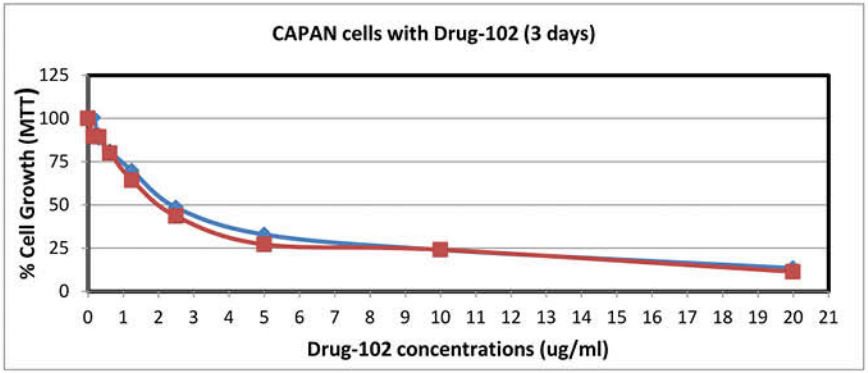
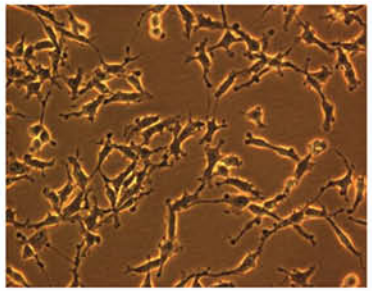


Figure 6

Importantly, cell growth never dropped to0% despite increasing concentrations of Drug-102 of even to 20ug/mL, indicating that the compound inhibits growth without causing cell death. This is important as compounds which cause death of cancerous cells can be highly toxic and will also cause death of non-cancerous cells. Our compound therefore makes for an ideal selective anti-cancer drug.

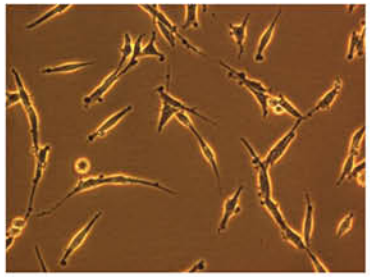
Modified saponins reduce cancer cell growth

Images of ES2 cells treated with Drug-101 (Figure 8) for 48 hours can be compared here to ES2 cells without drug treatment (Figure 7). The photos show that the number of cancer cells is reducedand the cancer cell morphogy has changed after treatment with Drug-101. The changed morphology (long spindle shaped and fewer attachment sites) indicates that the cells are not growing and thus would make an effective anticancer drug.



Images of ES2 cells (control without drug) at 48 hours after plating

Figure 7



Images of ES2 cells treated with drug-101 (10ug/ml) for 48 hours

Figure 8

Modified saponins inhibit DNA synthesis

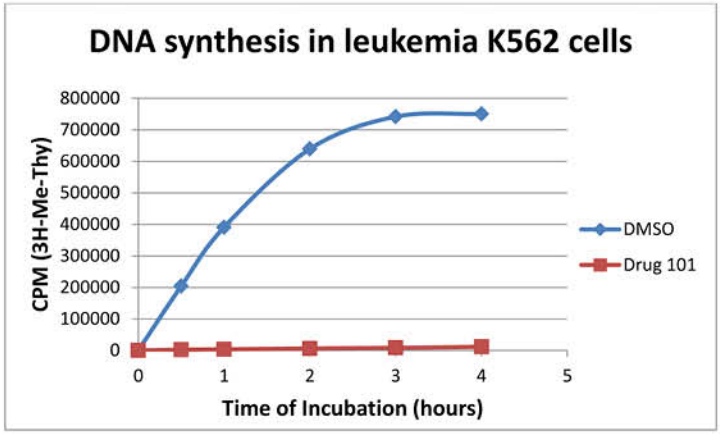


Figure 9

Figure 9 above illustrates that DNA synthesis in leukemia K562 cells is almost completely inhibited on incubation with modified saponin Drug 101(20 ug/ml) in leukemia K562 cells. After three hours of incubation, there is 98% inhibition (or 2% of DMSO control) of the DNA synthesis. This indicates that modified saponin Drug 101 is effective at treating leukemia and could developed into an anti-cancer drug.

Modified saponins halt the cell cycle

When K562 cells were treated with increasing dose of Drug-S (0-20 ug/ml) for three days, we found decreasing numbers of cells in G2/M phase from concentrations of 0.6ug/mL of drug S with a dose effect relationship noted to 20ug/mL. These results indicate that drug-treated cells were arrested in the S-phase and unable to enter into the G2/M phase of the cell cycle. Drug S could thus be developed into an effective anti-cancer drug.

Modified compounds are a solution for reducing drug resistance

A major impediment to cancer chemotherapy is the serious side effects produced by anticancer drugs, and the development of drug-resistance by the cancer cells. One of the ways to alleviate these problems is to employ multiple drugs with lower individual doses. These drugs preferably have different mechanism of actions and/or drug structures to reduce the chances of resistance.

For example Ara-C (cytarabine) is an approved drug for many types of cancers, especially leukemia (ALL, AML, CML). Cytarabine has a number of side effects, including nausea and severe myelo suppression. Based on our data, Drug-102 could be used in combination chemotherapy with Cytarabine. As can be seen in Figure 10 below, Drug-102 increases Cytarabine's efficacy in treating ovarian cancer by increasing inhibition of cell growth, allowing for reduced drug dosages to help alleviate unwanted side effects without compromising therapeutic efforts.

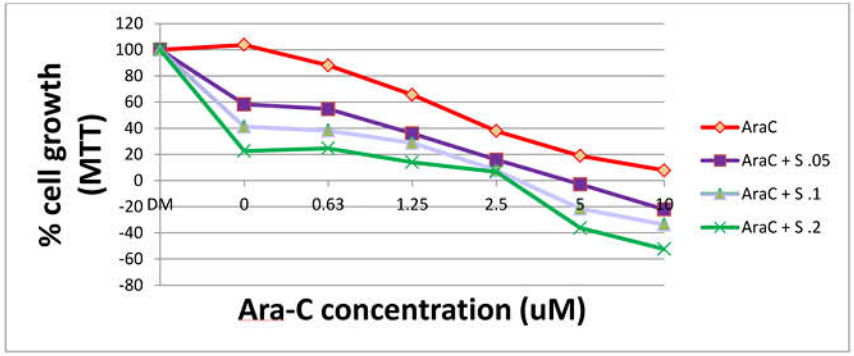


Figure 10

Daunomycin (Daunorubicin) is another widely used anticancer drug with major clinical applications in carcinomas of the breast, endometrium, ovary, testicle, thyroid, lung and in leukemia. Daunorubicin has side effects, including bone marrow depression and cardiac toxicity. Similar to Cytarabine, Daunomycin is commonly used in combination regimens with other anti-cancer drugs to reduce the dose of each drug to minimize side effects while maintaining the overall therapeutic effect. Our current studies indicate and support the idea that Drug102 could also be used with Daunorubicin (or its congener, Doxorubicin) in combination drug therapy. The special characteristic of reducing toxicity of modified saponin Drug 102 makes for an ideal combination selective anti-cancer drug.

Figure 11 (below) shows that Modified Saponin Drug-102 increases the potency of Daunomycin (DA) by 50% in inhibiting lung cancer cell growth.

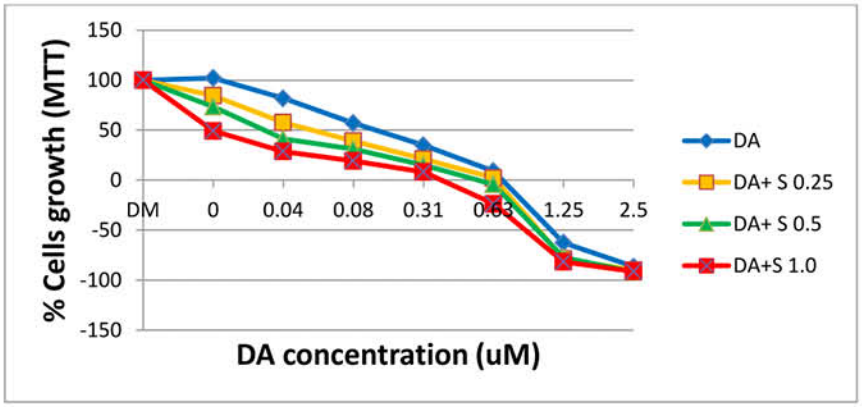


Figure 11

Campthotecin is another important approved drug used to treat leukemia. Our data shows that Drug 101 can be used to develop a treatment regime to allow for reduced drug dosages to alleviate unwanted side effects without compromising therapeutic efforts. In Figure 12below, where DMSO is the control, R1/Drug-101 (1uM) inhibits DNA synthesis to 44% of control (56% inhibition). Camptothecin (0.15uM, or C1) or (0.3uM , or C2) inhibits DNA synthesis in leukemia cells to 37% or 25%, respectively, of the control (63% or 75% inhibition). But when Drug-101 (1uM) is combined with either 0.15uM Camptothecin (R1+C1) or 0.3uM Camptothecin, (R1+C2), DNA synthesis is reduced to 23% or 16%respectively of the control (77% or 84% inhibition).These results indicate a higher inhibition of DNA synthesis can be achieved by combining administration of Drug-101 and Camptothecin, which makes our drug ideal in combination treatment regimes targeted against cancer.

Figure 12 below demonstrates the combined effect of modified saponin Drug-101 and Camptothecin in inhibition of DNA synthesis in leukemia cells.

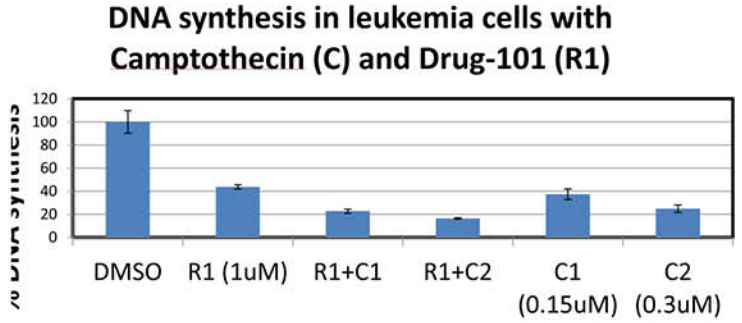


Figure 12

Concluding remarks

Over the past 10 years our project has succeeded in producing hundreds of thousands of new active saponins, with many of them shown tremendous potential to further develop into high-efficacy, low-toxicity target drugs as effective treatment for a wide range of cancers, including cancers of theovary, lung, pancreas, breast, liver, bladder, prostate, skin, bone, brain, blood cells, colon, skin, cervix, testicle, spleen, kidney, lymph, stomach and thyroid. We have successfully obtained multiple patents in the US, Europe, China, Japan, Australia, Korea, Canada for our compounds with still many more pending.

Our project was established at the Baylor College of Medicine in Texas, USA, to which we owe a tremendous debt of gratitude for its generous resources and supports.

Recently, the Innovation and Technology Bureau (ITB) was established in Hong Kong to promote the development of local innovation and technology industry, nurture local technology talents, and encourage the commercialization of R&D results from both private and academic sectors. We believe that Hong Kong has now created a favorable environment for the nurturing and facilitation to bring innovative projects to the market, one that is very attractive to us as we embark on our next endeavor: drug development and commercialization of our compounds. We would like to realize our goals and carry out the next stage of our work in our hometown - Hong Kong.We welcome any collaborations.

Chapter 6

TRADEMARKS ARE WORTH YOUR ATTENTION, BIOTECH COMPANIES!

Johnson Lam

Under our new era of knowledge-and-innovation-based economy, the biotechnology industry is like young bright players adding fuel to the growth of the global economy. This industry has a great potential to improve our well-being and quality of life, something so important for us.

Biotechnology companies typically spend tremendous resources in research and development in a continuous manner, to try to reap exponential profits and maintain their edge against the competitors worldwide. Going big and global is therefore a natural strategy to maximize interests. Against this backdrop, intellectual property protection requires extra attention from companies in the biotechnology sector.

When it comes to protecting the valuable intellectual property, biotechnology companies often give priority to their patents. An advanced-thinking and comprehensive global trademark filing strategies could, however, be equally important and vital. In this article, we will first discuss two key issues which is worth early attention for the business development of biotechnology companies. In the later part, we will briefly visit an ongoing Hong Kong trademark case involving biotechnology companies, which highlights the difficulties or risks in translating your valuable trademark rights into actual income streams.

A Springboard - Devising a "Good" trademark

Devising and designing a trademark is almost an art, where a good and impressive trade name certainly gives you a springboard.

Unsurprisingly, you will prefer that your trademark can help gain early attention from the customers and leave them an unforgettable remark. A conventional way is to devise a trademark indicating, to a certain extent, the qualities or characteristics of the technologies involved in your products and/or services; for example, Quick Dilution. Such a trademark, however, may be considered as descriptive and not allowed for registration. The rationale behind this is that other third parties would likewise love to use the "descriptive name" to describe the relevant products/ services, and therefore no exclusive rights should be granted to a single entity.

There are some ways to overcome this registration hurdle. First you can establish that the trademark was put into commercial use for a few years so that a secondary meaning has been acquired. Alternatively, when devising the trademark, you can select a suggestive (as opposed to descriptive) word. If an average customer will need to go through considerable mental gymnastics before associating the mark with the relevant qualities/ characteristics, it will be more likely to be considered as not descriptive and thus registrable.

A descriptive or suggestive trademark is generally weaker and more effort will be required to enforce your valuable trademark rights. By way of contrast, a self-coined mark which confers no dictionary meaning is strong or distinctive, and it is easier to register and to be enforced. Nintendo and Nokia are some well-known self-coined trademarks. Such a trademark does not carry any inherent meaning; hence a trademark owner has a greater opportunity to create a strong association between the mark and the corresponding products and/or services, and is afforded the broadest scope of protection against potential infringement.

A good trademark is also about localization. Some words may confer "special" meanings in a certain region which risk your reputation. In the marketing campaign for iphone 7, Apple Inc. cleverly adopted different Chinese taglines in the Greater China Regions to try to dilute and minimize the adverse meaning of "7" (foul language) in Hong Kong, where Cantonese prevails. Such sensitivity will give you an extra edge for brand-building.

1. https://qz.com/777628/the-slogan-for-apples-aapl-new-iphone-7-translates-into-this-is-penis-in-hong-kong/

Initial Public Offering and Strategic Planning of Trademarks

Given the upbeat rhythms, biotechnology companies are magnets to capital, elites and other resources. Coupled with the honest necessity for constant financial commitments on technological research, it is hard for a biotechnology company not to think big.

More likely than not, the Initial Public Offering ("IPO") should come into the picture at a certain stage of your rapid development. In the pre-IPO stage, the first thing you will definitely be advised is to secure, inter alia, comprehensive registration of your trademarks covering the scopes of businesses and the jurisdictions involved before any possible listing. This is indeed sensible. Without the relevant trademark registrations, your business activities may not be considered as legal and may reluctantly come to an abrupt halt upon third-party complaints and enforcement.

In this connection, you should also be aware that trademarks do not always mature into registration in a straight-forward manner, and that the approval processes in certain jurisdictions may not be as efficient as the business people could wish. In fact, it is not uncommon to take years to complete the whole trademark registration process. In Hong Kong, if you are not able to submit proof of adequate trademark registrations before the formal listing, a legal opinion is typically required to explain the situation to the satisfaction of the authorities.

Accordingly, if the IPO is something already in mind, you are strongly recommended to engage in an advanced-thinking strategic planning on trademark registrations. Otherwise, a possible delayed IPO process would be of course unwelcomed. Worse still, if a third-party may unexpectedly oppose your proposed listing, this could well be detrimental or even destructive to the IPO process. In Hong Kong, there was an instance where a company decided to omit its Chinese company name for the listing purpose in view of a last-minute IP challenge[2]. It will be a devastating experience if the IPO fails due to the basic trademark issues, with reputation injured and substantial consultation fees wasted.

2. http://www.aastocks.com/en/stocks/news/aafn-content/now.483650/ipo-news

A recent Hong Kong case and Commercialization

Glocalization is often advocated nowadays, where the multi-national corporations are urged to "think globally and act locally", and give due weights to both the global and local considerations. Close cooperation and collaboration with the local partners and associates are therefore inevitable and increasingly important. Yet, commercial cooperation is never straightforward, and is highlighted by a recent Hong Kong case *Nerium Biotechnology, Inc. & Ors* v *Nerium International, LLC & Anor HCA* 1188/2016 (the "Case").

This is an ongoing case and the facts are still hotly disputed and unsettled. To summarize, but subject to proof, the Plaintiffs claim to be an international research and development company incorporated in Canada in 2006 and subsequently expanded its businesses globally. It is the Plaintiffs' case that they looked for other means of marketing and decided to pursue multi-level marketing with the Defendants in 2010. The 2nd Plaintiff owns 30% of the 1st Defendant. They signed an agreement, which further contemplates the future execution of a Distribution and Licensing Agreement to "provide for the use of the intellectual property, formulation of the Product Line, the faming, storage, processing and manufacture of the specific products that comprise the Product Line etc". However, such a further agreement was never signed between the parties. The cooperation did not go well. According to the Plaintiffs, the Defendants, without the Plaintiff's consent, developed a new line containing the Plaintiff's trademarks. The Defendants even redesigned the website to remove extensive references to the Plaintiffs.

On the other hand, according to the Defendants, the 1st Defendant should be the exclusive marketing channel for the Plaintiff's products. The Defendants spent its own resources to design and develop a new logo, and decided to display the 1st Defendant's name more prominently on all of the packaging as the general public regard the 1st Defendant as the sole trade source for these products. The Defendants also say that the Plaintiffs have been intentionally overcharging the 1st Defendant for the supply of the products.

This is not the intention of this article to make comments on the unsettled facts of the Case. A lesson well learnt, nonetheless, is the very importance of execution of a comprehensive contract among the parties right at the beginning, where numerous practical and legal issues should have been in contemplation with meeting of minds. Rights and obligations of the parties should have been carefully delineated. Any

minimum ordered quantity required? Who should be able to set the retailing prices? Who should apply for and be responsible for the costs of trade mark registrations? Who should control the proceedings of any possible trade mark infringements, either suing others or being sued? What will the post-termination arrangement, especially in relation to the trademarks?

This world is changing unprecedentedly fast, so dynamically that a well-drafted contract is simply not good enough. Subsequent review of the accommodation to the business development, as well as regular communications among the parties to avoid souring relationship, would be the key to a sustainable success. In terms of trademarks, before you decide to go global, or create a new line of business, it is wise for you to review again your trademark portfolio whether it provides you with sufficient trademark protections in different jurisdictions, and attend new trade mark filings if so required.

Conclusion

Intellectual property is indisputably crucial for the business development of a modern company. The technology-driven biotechnology companies are of no exception.

While patent protection often "steals" the attention from the companies in the biotechnology sector, trademark protection should not be taken lightly as well. This article has highlighted some issues very real to the biotechnological companies, especially taken into account that global expansion and IPO are likely involved in the sustainable growth thereof. An advanced-thinking strategic planning of trademark protection, together with well-drafted contracts and regular reviews, will lead to healthy development and successful commercialization.

Under tailor-made care and training, one day young bright players will become world-class glittering stars!

Chapter 7

A ROADMAP FOR THE HONG KONG BIOMEDICAL TECHNOLOGY INDUSTRY

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Abstract

In the last two years, important changes that favorably impact on the Hong Kong biomedical industry have occurred along with the establishment of the Innovation and Technology Bureau since January 2016. These changes, both from the external environment including the CFDA regulatory reform and the internal environment where new funding schemes for innovation research have arrived among others, have helped transforming the landscape and outlook of biomedical technology in Hong Kong. With a 1.4 billion population Chinese market that is practically within reach, Hong Kong is uniquely positioned to connect the rest of the world to this lucrative Chinese market and vice versa by supporting the top Chinese biotech and pharma firms to gain access into the global market serving as the "super connector". The ultimate goal is to improve on the manufacturing GDP and to regain the manufacturing momentum for Hong Kong enterprises, i.e. re-industrialization that will sustain economic growth and future prospects for the younger generation. This chapter summarizes some of the steps and directions that Hong Kong may consider in order to bring this finance, tourism, services and trading power house city into the biomedical technology domain.

A] Better be lucky—changes that favor biomedical technology industry in Hong Kong.

We have summarized some of the fundamental requirements for Hong Kong to become successful in this highly regulated biomedical technology industry in the previous volume; factors include regulatory affairs, funding schemes and R&D personnel. The establishment of the Innovation & Technology Bureau (ITB) in November 2015 is a first step that would co-ordinate science and technology development in Hong Kong. Following right after was the establishment of the Hong Kong Academy of Sciences where the Founding President, Prof. Lap Chee Tsui and 26 Founding and Senior Members represent the academic scientific excellence providing relevant advice to the government. In the subsequent two policy addresses by the Chief Executive of Hong Kong SAR in 2016 and 2017, new and generous funding schemes are being unveiled that would fuel innovation and technology development. The operating principles of these funds are clearly directed to support applied research and to nurture strong academia-industry-government partnerships. The currently available funding schemes are listed in Table 1. Simultaneously, there is also a craze of biotech and healthcare funds searching for investable opportunities in Hong Kong. These investors, ranging from angels for startups to acquisition activities for more mature companies, provide another source of financial support for the biomedical industry. Finally, similar to the Australian system, it will certainly provide another surge in funding if the Hong Kong Stock Exchange could consider introducing new listing rules that may allow companies to be listed for public offering before revenue and profits occur by establishing a new GEM 2.0 Board. This would be particularly helpful to the biomedical technology companies as it usually takes a longer time period for products to move into the market.

Table 1. Funding Schemes from Innovation Technology Bureau
(source: www.itf.gov.hk)

Type of Funding scheme	Description	Funding Amount (Max.)
R&D Cash Rebate Scheme	• To reinforce the research culture among private companies and encourage them to establish stronger partnership with local public research institutions • Companies can receive cash rebate equivalent to 40% of its expenditure in 2 types of applied R&D projects: 1) Projects under the Innovation and Technology Fund (ITF) (ITF projects); and 2) Projects funded entirely by companies and conducted by designated local public research institutions ("Partnership projects")	**HKD $200 million**
General Support Programme (GSP)	**Internship Programme** • Each ITF project can apply for two interns (graduates from local universities) conducting R&D with a monthly allowance. • Starting from 1 Feb 2012, the monthly allowance has been increased by nearly 20%. • Maximum internship period is 24 months	Internship allowance: **HKD $14,000** for graduates with a Bachelor degree **HKD $16,500** for graduates with a Master or higher degree
Enterprise Support Scheme	• To encourage the private sector to invest in R&D • Project period should not be longer than 2 years. • Recipient company own all intellectual property rights • Recoupment of Government's contribution is not required. • Benefit-sharing of commercialized R&D results would be non-mandatory. • Can apply for Internship Programme to hire up to 2 interns. • Can apply for R & D Cash Rebate Scheme to receive a cash rebate of up to 30% of the company's expenditure in the project. • In the best case scenario, the company only needs to invest HKD $292,250 for a HKD $1.3 million project (i.e. ~22.5%).	**HKD $10million/** project on a dollar-for-dollar matching basis.
Public Sector Trial Scheme (PSTS)	• In general, the Funding limit: 50% of the actual cost of the applied R&D projects supported by the ITC. • To speed up the process of industry adoption of R&D outcomes, the funding ceiling is increased to 100% of the actual cost of the original R&D project(s) supported by the ITF under the following conditions: 1) The PSTS project must be undertaken/coordinated by the R&D centers. The R&D Centre concerned may collaborate with universities and other research institutes in conducting the actual trail. 2) The Applicant (i.e. R&D	In general: 50% of the actual cost of the applied R&D projects supported by the ITC But can reach 100% of the actual cost with conditions 1 & 2.

	Centre) would need to demonstrate the project would bring wide community interest (e.g. benefits not restricted to a particular sector or product) and justify the need for a larger budget. • Introduced on a trial basis and limited to R&D-initiated projects	

While funding is extremely important for innovation and research, for a highly regulated industry like biomedical technology, the regulatory environment is equally critical. For Hong Kong, this environment may be impacted by China's regulatory agencies. In the last couple of years, several changes have occurred in China with the most important regulatory body in the healthcare sector, the Chinese Food and Drug Administration (CFDA). Recognizing the inadequacy in the therapeutics approval processes, the CFDA has undergone swift changes from organizational infrastructure to operation principles, while maintaining transparency and communications. To this effect, the CFDA has close ties with the Hong Kong Food and Drug Bureau, the two medical schools and even private hospitals, e.g. HK Sanatorium Hospital, to promote professional interactions. In 2016, the CFDA announced plans to raise the bar for drug approval and demanded better data quality requirements in bio-equivalence measurements for the drugs seeking approval, including generic drugs. In addition, the CFDA has suspended all cell therapy commercialization activities in China in order to formulate the proper regulatory guidelines. Separately, the CFDA has accredited two university hospital clinical trial centers in Hong Kong for phase 1 activities, thereby rendering the clinical data generated in Hong Kong from the two teaching hospitals, Queen Mary Hospital and Prince of Wales Hospital, to be accepted for drug approval and marketing approval purposes in China. The CFDA also collaborates with the two teaching hospitals to set standards for bio-equivalence measurements that would vitalize the clinical trial study environment in Hong Kong. This complements the desire of the CFDA to improve on the quality of the regulatory assessment processes. Unfavorable stories such as juvenile subjects suffering from serious health hazards after receiving vaccines of below-quality standards and the flood of poorly regulated cell therapy clinics in China leading to fatalities of those receiving treatments, triggered the CFDA to have radical changes in the regulatory system, including a halt to cell therapy commercialization in 2016. Hong Kong was thus uniquely positioned to work with the CFDA and other global agencies to design and develop the regulatory framework for advanced therapies including cell therapies. This is especially timely since an international standard of pharmaceutical manufacturing integrating with regulatory, the Pharmaceutical Inspection Co-operation Scheme PIC/S, first commenced in 1995, where Hong Kong [joined Jan 2016] and many other countries are member countries/ regions whereas China is not. Under PIC/S, the regulatory responsibility in accrediting a pharmaceutical manufacturing facility and its product resides in the local government, and once approved, the product should be able to reach any other country within the PIC/S system without the necessity of quality re-assessment by the receiving PIC/S country. Thus, all these changes, along with the government support on innovation, STEM education and entrepreneurship converge to accelerate the biomedical technology industry development in Hong Kong.

B] Pursuing the Appropriate Technology for Revitalizing Manufacturing in Hong Kong.

With the regulatory and funding environment becoming more favorable, the next challenge is to identify those technologies for pursuit where Hong Kong would have a strong competitive edge while providing a fair chance to revitalize local manufacturing activities. These technologies may have the following characteristics:

1. be able to generate highly valued quality products or services, in order to capitalize on the IP protection and to produce high-paid jobs and businesses that can sustain the high cost of living in Hong Kong,

2. be able to survive the realistic limitations of space constraints for manufacturing or service provision in Hong Kong,

3. be a world-renowned technology that can capitalize on the global market, especially the China market, or a new technology where global leadership has not been established,

4. be able to utilize the local supply of talent pool for sustained business operation.

Since 2014, two advanced technologies, Genomics Medicine and Regenerative Medicine were initially targeted based on: the world-class scientific leadership, the talent pool that we have, the intellectual property that has been accumulated, the high impact on healthcare, the revenue generated and the official recognition of the

clinical data from Hong Kong (as deriving from a Chinese ethnic population facilitates the growth of genomics-based diagnostics industry in Hong Kong).

Molecular Biology gave rise to Genomic Medicine and has a long history in Hong Kong, stemming back from the 1980's when Prof. Y.W. Kan of the University of Hong Kong (HKU) and the University of San Francisco worked relentlessly on thalassemia with others such as Professors Vivian Chan, T.K Chan and J. Tam of HKU. Similarly, seminal work on hepatitis B conducted by Professors C.L. Lai, A. Lok, Dr. H.J. Lin and others such as Prof. M. Lung [virology] and Prof. K. Cheah [bone metabolism] helped establishing a solid molecular biology foundation in Hong Kong. The arrival of Prof. L.C. Tsui and others further expanded the expertise pool in this exciting biology. The marvels of 'liquid biopsy' initially discovered by Prof. D. Lo in the 1990's, and further developed by the team comprising Professors R. Chiu and A. Chan of The Chinese University of Hong Kong (CUHK) has taken Hong Kong genomics biology to its pinnacle. Subsequent addition of molecular biologists and genomics scientists [e.g. Professors S.Y. Leung, Y.L. Kwong and F. Leung of HKU, Prof. D. Leung of Hong Kong University of Science and Technology (HKUST), Professors M. Yang and S.H. Cheng of City University of Hong Kong (CityU)] ascertained the leadership pool and training available to Hong Kong. It is thus not surprising that based on the genomic technologies and intellectual property thereof, renowned companies such as Xcelom and Berry Genomics focusing on noninvasive prenatal testing, Sanomics focusing on lung cancer early diagnostics, Cirina focusing on early cancer screening, Angsana and GenEdge focusing on allergy testing, Govita focusing on depression test, Kingmed focusing on molecular diagnostics and infectious diseases, and many other companies were established receiving intense attention and interest from investors.

Likewise, the promise of stem cell therapy to cure the incurable diseases also attracted strong academic participation. Professors H.F. Tse, P. Tam, S.Y. Leung and B. Chan of HKU, Professors W.Y. Chan, K. Lee, R. Duan of CUHK, Prof. K. Yung of Baptist University, Professors T. Cheung and N. Ip of HKUST are some of the lead scientists on stem cell biology and clinical research. This inevitably has attracted other global institutions to establish in Hong Kong for collaborations. Examples include Karolinska Institute and Guangdong Institute of Biomedicine and Health to date, along with a number of stem cell companies such as BioCell, Aquest, Mononuclear Therapeutics, Oper Therapeutics, TGD Life Sciences and Novoheart, establishing in Hong Kong. It is expected that some of the technologies will be heading to clinical trials in the near future.

As Genomic Medicine and Regenerative Medicine technologies are being developed, new technologies for the future are being identified. A compelling example is the Genome Editing or CRISPR technology that is of special significance as Hong Kong announced in December 2015 the first successful clinical application in metachromatic leukodystrophy [a form of rare leukemia with genetic mutation] in Asia was conducted by The University of Hong Kong, Zhongshan University and National Taiwan University, marking her leadership position in clinical practice. This technology, when combined with stem cell biology and the latest epigenetics analyses [gene regulation], will have major impact on multiple applications from clinical to agricultural aspects.

Following some of the mishaps in China, where lethality occurred because of the use of substandard vaccines and in view of the logistics and supply chain limitations in the current peptide/protein based vaccines, new vaccine modality is being sought. A disruptive technology whereby the vaccine is based on RNA instead of peptides or proteins may soon become available. This vaccine modality will not require the cold storage that is critical in the previous versions and thus will have supply chain and logistic advantages while offering additional quality assurance once efficacy is verified. Because of its rapid turn-around time from inception to product for testing, it is perfectly positioned to serve the infectious disease arena where the viral genome can rapidly mutate, e.g. influenza, and even personalized medicine as cancer vaccines. The acceptance of the clinical data in Hong Kong by the CFDA and the proximity to the origin of influenza are strong reasons for such technologies to establish in Hong Kong while capitalizing on the Chinese and Asian market.

A third potential is Bioelectronics that integrates biology/physiology with electronics and internet communication technology. The products can range from wearable to implantable device that may offer both diagnostic monitoring and even treatment solutions. As this technology encompass expertise from multiple disciplines, in a condensed small city like Hong Kong that facilitates technology integration, it may be most suitable for R&D and pilot testing of such devices where 5G internet applications, cloud data storage and artificial intelligence analyses of data can be readily conducted.

C] Preparing for the future

1. Biologics and Cell Processing Pilot Batch Facilities

As the two clinical trial centers in the medical schools are accredited by the CFDA and accepting clinical trial data for registration and market approval purposes, there is a flurry of trial projects to be conducted in Hong Kong. While additional trial centers

with similar quality of clinical practice and integrity are being sought to accommodate the influx of clinical trials, it is pertinent to capitalize on this momentum and start considering the follow up activities, one of which is the provision of quality drug batches for clinical trial purposes. These clinical trial drug batches may be prepared under GMP conditions but not necessarily in a manufacturing scale, and the specific facility for producing such drug batches [~100 g] is the Pilot Batch facility. They are critical in the drug development value chain and are of particular importance especially for biologic drugs, as the biologics demand stringent storage and transportation conditions to avoid quality risks. While manufacturing plants for biologics are readily available in Asia, Pilot Batch facility for preparing GMP quality biologics for clinical trial purposes are scanty. Thus, if Hong Kong were to conduct clinical trials including biologics, Hong Kong would be able to offer additional services if she were able to support the biologic pilot batch production to supply the delicate biologic drugs locally for trial purposes.

At the same time, cell therapy is also reaching the clinical development stages whereby GMP facility would be required to generate the cells, be it autologous or engineered cells, to be infused into human subjects. Since these are new activities, academic and private institutions are trying to establish the cell processing facility under GMP conditions to facilitate academic clinical research and clinical trials activities. The Pilot Batch facilities will offer unique training opportunities for local talents to learn the professional biologic and cell processing manufacturing knowledge and skills. This type of expertise is not available in textbooks or university courses but is a unique on-the-job training opportunity. Such knowledge will enable bridging into larger scale manufacturing and prepare the talent pool for such activities when re-industrialization happens.

It is important to note that Hong Kong is also nicely positioned as a member country/region in the new international PIC/S drug manufacturing system. The trial batches, biologics or cells, produced in Hong Kong are also applicable in the other 50 or so PIC/S member countries. Unlike the regular manufacturing plants, these Pilot Batch and cell processing facilities do not occupy a lot of space, a factor that suits Hong Kong. In parallel, GMP-grade facilities for producing Traditional Chinese Medicines would have the proper guidelines and adequate expertise for bringing Chinese medicines into indisputable world-class production quality in Hong Kong. It would be a unique opportunity for Hong Kong if these pilot batches or even manufactured products from Hong Kong would be accepted for clinical trial and registration purposes by the CFDA. That will offer another unparalleled advantage for the biomedical industry in Hong Kong.

2. Personal healthcare

Bioelectronics devices are expected to make a huge impact on healthcare and personal care. The wearable and implantable devices would complement classical diagnostics and labor intensive clinical monitoring of the patients/subjects and even boasting their potential as the third important medical treatment module other than medicine and surgery. These devices are also expected to be connected to the Cloud data storage/analyses via Information & Communications Technology systems offering continuous longitudinal monitoring opportunities along with cross sectional population big data analytics opportunity. These datasets would be critical for personalized medicine and even the forthcoming home care, that may steer in parallel towards preventive care ultimately. Together with the 'OMICs' data collected from individuals, these digital data will represent a new generation of health data that will be a powerful tool for the future health care systems including preventive care. Since the amount of data involved will be huge, artificial intelligence and super-computing will be recruited for meaningful and speedy analyses. When combined with the current electronic medical records for the Chinese in Hong Kong, it will become a comprehensive Chinese healthcare database. Once and if, the Hong Kong dataset were integrated with the south China region such as the 11 cities in the 'Bay Region', it will represent the first Chinese healthcare database that offers unlimited opportunities, whereby a new industry based on health informatics could be generated in Hong Kong encompassing specialties such as bioinformatics, biostatistics and, capitalizing on the well- developed computing and communications infrastructures, free information flow and international advantages that Hong Kong offers.

3. Talent Pool and Professional Training

With all these promising technologies and projects in place, a critical piece for the implementation is the talent source. Clearly Hong Kong has many excellent tertiary academic institutions training quality scientists and fueling the innovation project pipeline. It has also been a norm that Hong Kong would recruit talents from nearby or global regions to satisfy the practical needs. Yet on closer examination, some inherent hurdles may have to be overcome to ensure the steady stream of talents and innovation can be translated for commercialization.

First, the university curriculum is targeted towards scholastic education, and not necessarily for vocational training purposes. Thus, a closer look into the life sciences curricula in Hong Kong reflects a clear gap in the skills and knowledge sets that the

modern biomedical technology industry is looking for. A simple example can be drawn from the exponentially growing genomic medicine field that demands talents on genetic sequencing, gene editing, bioinformatics, system biology and even genetic counselling. Yet, in all of the current curricula of the Hong Kong institutions, professional training in these areas is not included. Thus there is a mismatch, whereby the companies are looking to recruit candidates with practical experience but in vain, while graduates are looking for jobs but are also disappointed. A quick fix is to implement postgraduate training courses targeting specific areas, and also to add the specific highly sought-after courses into the undergraduate curricula. Finally, accreditation or certification of these individuals in the relevant fields should be included to ensure quality in the deliverable and also enhancing the social hierarchy of these young scientific talents. The current limitation to qualified Medical Laboratory Technicians [MLT] for handling human samples is appreciated, but scientists spending years in the research laboratory that are equally qualified and perhaps even beyond simple specimen handling, should also be entitled to conduct such processes. This is especially true for advanced sciences such as regenerative medicine and genomic medicine. The current Medical Laboratory Technicians who are trained to perform in diagnostic pathology laboratories, may be limited academically and professionally to handle the advanced subjects, but those who are technically capable, e.g. in academic research laboratories, may be inhibited by the lack of the MLT certification. This irony can be easily resolved by allowing qualified personnel to be entitled to operate on the new advanced science-based activities such as immunotherapy, genomic medicine, tissue engineering and bioelectronics, likewise to offer enrichment professional courses to the MLT for their advancement. It is pertinent for Hong Kong to provide a sustainable source of human talents in the biomedical technology area to meet the demands of the new therapies and technologies that are rapidly coming into place.

Secondly, although the academic scholastic research in Hong Kong academic institutions have earned global recognition with a strong publication record, few of these elegant research have been translated into commercialization despite grant incentives and a strong push from the government. This could be attributed to the scholastic mindsets of the professorial scholars who are in a secured university employment system and disinterested in commercialization. In addition, the Technology Transfer Office and Knowledge Transfer Centers in the universities have largely failed to guide the professors to translate research, nor be able to effectively connect to the mid- and downstream industry partners and investors. The vicious outcome for the lack of biomedical technology industry in Hong Kong for the last thirty years is that it fails to produce the relevant personnel in the key areas. For a profession that is not taught in any of the university curricula worldwide, Hong Kong has to bring in the key talents to bridge this gap, to enable sustained growth from implementation, administration and strategic consultation purposes. In the short term, the various university technology transfer offices can assimilate their limited resources in specific areas to offer cross-university program supervision and co-ordination to facilitate translational research.

4] The He Tao 'Loop'

The boundary between Hong Kong SAR and China is the Shenzhen River. There existed a region where the river was flowing in the shape of 'U'. In 1997, the bending river was straightened out and the Chinese government agreed that the new piece of land south of the river belonged to Hong Kong. In January 2017, the Chinese government officially reiterated that announcement and the Hong Kong government also announced that the land would be devoted to innovation and technology development in collaboration with Shenzhen. As the land will be ruled under Hong Kong law, it would be operated by a new subsidiary company of the Hong Kong Science Parks Corporation. While the detailed planning of the utilization of this valuable piece of land is still being drafted and ideas were solicited, some possibilities specifically where the unique features of this 'land' can fit into biomedical technology development that complement the existing infrastructures in the Hong Kong Science Parks are listed below for consideration.

Four initial pillars are being envisioned, each capitalizes on unique advantages that Hong Kong can offer and would provide major impact towards Hong Kong/China/regional health care beyond entrepreneurship and monetary return. These pillars though are standalone specialty that will have lots of cross-talks that would produce synergy among themselves.

a] Brain Institute

The brain and the nervous system are among the least understood body system albeit multiple grand project efforts that have been initiated worldwide. It represents a chest of valuable knowledge that would help not only to battle the incurable neurological disorders and neurodegeneration diseases but also to spark new inventions based on this natural marvel. To distinguish this institute from similar ones in China and the USA that mostly study neurology or neurosciences, this institute will focus on neurodegeneration, partly to capitalize on the local expertise. It will be led by a dozen or world-class neurologists and neurobiologists to pursue on translational research around neurodegeneration. These scientists should all be associated with a local

academic institution, but the Brain Institute will be operating independently of any university. Funding could be provided by the government, Hong Kong, Shenzhen or even China, private donations or partnerships with the industry that can serve as downstream collaborators. To support 40 laboratories operated by some of the top scientists in the world, an initial budget of USD 200M is anticipated. Such an institute will complement the brain project in China, and will likely contribute to a global leadership position offering major discoveries and impact.

b] Advanced Therapies

Successful translation of the research outcome from the Brain Institute is essential. Thus the second pillar will focus on bringing the advanced therapies and modalities to health care. These can be in the form of new vaccines, regenerative medicines, gene therapies, genome editing, bioelectronics [wearable or implantable], new traditional Chinese medicines, etc. As these new treatments reach the clinical trial stage, the manufacturing requirements and approval principles will need to be established. The initial themes for this pillar can be on neurodegeneration and health issues of regional interest, e.g. cancers, infectious diseases and ageing care.

c] Health Informatics and Artificial Intelligence

As genome sciences become more versatile and sophisticated, unfavorable health conditions can even be predicted ahead of time leading to predictive and preventive medicine. This pillar will enforce the integration of genomic data from DNA sequences to epigenetics and other 'OMICs' data that together, along with other behavioral data and body signs as measured by the wearable and implantable device, will form a new generation of health data. As the population in Hong Kong and Southern China are mainly made up of Chinese ethnicity, this dataset will represent a unique and comprehensive health dataset for the Chinese populace. It will be the anchor dataset for the entire Chinese health system and be able to serve as the leading template to integrate/compare to data obtained from other Chinese cities/provinces and hence to even produce the final integrated health record for China. The software system, data storage and data analyses involving bioinformatics beyond statistics and data sciences will generate a new industry that possibly will utilize artificial intelligence in the process, thus the new artificial intelligence will be included in this pillar with specific applications to health care from genomics data analyses to personal health monitoring. It is also expected that new biomarkers for disease diagnosis and monitoring along with commercialization of diagnostic tests will be part of the translational output from this pillar that will be closely associated with those pillars described above demonstrating synergy.

d] Analytical Food Sciences and Certification Sciences

This pillar would capitalize on the unique location of the land in the 'border' region between Hong Kong SAR and China. It will focus on the food safety inspection and certification services, from poultry and meat to vegetables that will be transported between Shenzhen/China and Hong Kong SAR. Expanding this unit further, it may also include the certification of traditional Chinese medicinal herbs based on advanced analytical sciences including plant genomics. Since these activities may involve regulatory bodies, to facilitate the advanced therapeutics continuum, a joint regulatory unit including regulators from Hong Kong SAR and the CFDA and even global regulators may be established here to lead the region in advanced therapeutics regulatory activities.

D] Final words

Clearly, the environment for developing innovation and technology, especially for the biomedical technology, has been exciting in the last several years in Hong Kong along with positive changes. There is still a long way to go for Hong Kong to become the biomedical technology center for Asia. With close collaborations among the government, industry and academia sectors, ample funding, appropriately trained work force, inspired entrepreneurs and the determination, Hong Kong will become a pearl of the East in innovation and technology, contributing to China, Asia and unmet needs of global healthcare.

Chapter 8

EVERYTHING YOU WANTED TO KNOW BUT WERE AFRAID TO ASK ABOUT LAUNCHING A BIOTECHNOLOGY BUSINESS IN HONG KONG

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Abstract

The notion of turning scientific discoveries into applicable technologies has become a trend in academia. This is no exception in Hong Kong. In fact, the Government of Hong Kong has been allocating resources in recent years to promote the development of innovative and high-technology (high-tech) industries, including biotechnology (biotech) industry. Local universities also have become more active in translating their research outputs into transferable knowledge and technologies. Owing to different reasons, one may deliberate on setting up research and development (R&D)-based biotech business in Hong Kong. Through the conversation between a veteran scientist (Prof. Al) and a scientist-turned-biotech entrepreneur (Dr. Pal), you can have a glimpse on the concerns and potentials of developing biotech industry in Hong Kong. You may find something helpful or familiar with.

So the story goes …

Al: I have been a research scientist in biomedicine my whole life. I believe some of my findings are good enough to be turned into usable technologies. How can I make it happen?

Pal: That's wonderful! I am assured you have discovered something great just by looking at your prolific publication record. You told me before you have patented some of your research outputs together with your university. Have you ever thought of starting a biotech business to turn your discoveries into technologies that people can use?

Al: I did think about that. However, I don't quite know how to begin with. You know, I spent most of my time exploring and discovering the unknowns, and I am not quite a businessman. I know there are companies discussing with our technology transfer office on licensing my patented technologies, but I don't think it has led to anything solid yet. It is already exciting just to dream on turning my own discoveries into something people would recognize. Can you give me some suggestions?

Pal: Sure. The first thing, of course, is to incorporate a company here in Hong Kong. You will need to identify the market of your technologies, what you want to sell (for instance, a product or service), assemble your R&D team and production scheme, and to establish your sales network eventually. If you plan to use your patented technologies, you will need to obtain from your university the right to use them for commercial purposes. Certainly, you will also need capital and may wish to find an office or laboratory to start your business. I am sure the technology transfer office and entrepreneurship center of your university can offer assistance and support to you in this endeavor. Don't they have funding to help professors and students open their startups?

Al: Oh really? I need to check. Talking about that, I guess I can consult Professor Sam from the business school. He is also the director of our entrepreneurship center. I attended his talks on marketing principles and strategies some time ago and I found the topics very interesting. I never thought of dealing with business stuffs before, but I guess I can seek advice from him now.

Pal: That's cool!

Al: We all know starting biotech and other high-tech businesses is a common thing in the US. They have a large market and a lot of investors who are willing to take risk. Are you sure we can do it in Hong Kong? No offense, I mean, I know you are doing biotech R&D business here.

Pal: It's alright, Al. It may sound difficult but it is not that difficult if you do it right. Having said that, there are certain things you need to pay attention to if you plan to launch a biotech business in Hong Kong, I will come back to these later. I would like to say Hong Kong has everything she needs for developing biotech industry. As you know, biotech industry is a knowledge-based industry. The demand for physical space, in other words land use, is little. Instead, the availability of personnel with the right knowledge and skills as well as appropriately-equipped laboratories and workspace are essential to success. I believe your students and graduates will easily fill up a classroom if I call on your behalf a home-coming gathering in a week, doesn't it?

Al: Exactly! Let me see, I have trained so far 20 MPhil students, 12 PhD students and co-supervised almost the same number of PhD students with other professors, and probably more than 30 summer students. Some of them stay in the academia locally and overseas, while the others pursue their careers in different business sectors and a few of them are working in government departments.

Pal: Six of our local universities offer life science-related curricula at both undergraduate and postgraduate levels, which should serve as a steady supply of trained human capital to local biotech industry. Two of the universities, including the one you work at, have affiliated medical schools as well as accredited clinical trial centers to facilitate biomedical research from basic to clinical and translational aspects. Quite a number of the professors produce world-class scientific discoveries and technological advancement. You surely are one of them, aren't you?

Al: You know I won't say no on this, ha-ha. Several of my publications are highly cited by other investigators in our research area. I am confident our science is not inferior to those from the more affluent countries where government expenditure on education related to STEM (Science, Technology, Engineering and Mathematics) subjects is greater. Of course, I hope our government would inject more money to support us to do even better science here in Hong Kong. We spent too much time on writing grant applications. We can actually devote the time on our research works and their translation.

Pal: Totally agree. Another point to touch on is something we all know about Hong Kong. We have a simple taxation system and the tax rate is low when comparing with a lot of places in the world. In fact, Hong Kong has been ranked the freest economy in the world for many years1. We have a stable society in general. We have a legal system that upholds the rule of law and protection of intellectual property rights. These are attributes that have been attractive to many foreign businesses.

Backed by these attributes, the close geographic proximity to mainland China puts Hong Kong in the best position to connect both the Chinese and global biotech and pharmaceutical markets. China has become the third largest pharmaceutical market in the world and has been the fastest growing market in the industry2. The demand for pharmaceuticals, healthcare products and medical devices and services in China is expected to increase with the rise in child birth owing to the lifting of "one-child" policy and the emergence of aging populations3. The commodities in demand are all biotech-related. You can see how large the business potential is.

Al: Everything sounds attractive and motivating indeed. However, I don't think I have the capital to start a biotech business here though …

Pal: There is a funding program called "Technology Start-up Support Scheme for Universities" managed by the Innovation and Technology Commission (ITC) of the Government. This program aims at supporting university teams of professors, students and alumni to start tech-based businesses and commercialize their R&D results4. I believe some of your colleagues in other faculties have founded startups with the aids from this program. Like what we discussed earlier, you can check with the technology transfer office and entrepreneurship center of your university. They may have seed money for professors and students to apply for launching their startups.

To further support these teams' endeavors, I hope the universities would create extra workspace for them to operate if they have not done so. You know, it may not be easy for startups to afford renting a workshop outside. The resources that are present in the universities can actually be used to foster these teams at their beginning phase. I think the best working places for them will be the existing research laboratories and student laboratories. I would like to see the relevant departments can make these facilities accessible to student and

professor entrepreneurs, as long as the daily research and teaching activities are not interrupted.

Al: Yes. It would be regretful if we have the resources around but cannot make full use of them to do more.

Pal: We shall see. On another note, additional funding programs are available from the ITC that startups and small and medium enterprises (SMEs) can apply for5. There are also privately funded incubation programs available for technology startups that have a launch plan or simply an innovative idea or business solution. In fact, the Hong Kong Science Park has an incubation program for biotech startups too. Have you heard about that before?

Al: Right, you have a laboratory in the Hong Kong Science Park. How is everything there?

Pal: It is a wonderful place to work. The Hong Kong Science Park is located along the Shing Mun River, overlooking the mountains. The scenery is pretty. Office and laboratory buildings are within walking distance, yet there is a lot of open space on campus. We can enjoy sunshine, have a walk or bike around easily.

In terms of strategic development, the Hong Kong Science Park has five major focus areas, namely biomedical technology, electronics, green technology, information and communication technology, and material and precision engineering.

There are things that I like working in the Hong Kong Science Park. First of all, they offer a chain of supportive services to both incubatee companies and SME tenants. For instance, talks and seminars are constantly organized to cover a variety of topics such as protection of intellectual properties, business strategies, management skills, etc. Very often, the legal and intellectual property firms on campus or outside are invited to offer free consultation sessions. These events are very helpful to people like me who are not trained as businessmen at the first place. I go to these talks to learn and to make new friends.

To reduce the financial burden of startups, incubatee companies can enjoy a much discounted rate on office and wet lab rental and are eligible to apply for additional financial assistance. The Hong Kong Science Park also provides management, promotion and investment support. For example, they organize business matching events between incubatee companies and potential investors as well as technology partner companies; they have connection with angel investors and venture capitalists to help incubatee companies raise funds. The Hong Kong Science Park also has its own Corporate Venture Fund available to us to apply for. These are all additional channels that you can explore to raise capital and reduce financial cost for your biotech business.

In terms of infrastructure, the buildings on campus are well maintained. A lot of the wet lab facilities are ready-to-use. If tenants wish to fit out their laboratories in accordance with their operation needs, there are also bare-shell units available for rental. Incubatee companies and SME tenants have access to the Biotech Support Center, which is core facility housing different major life-science R&D equipment. We often use these instruments in our R&D work and the charge is very reasonable. That helps a lot in terms of budgeting and convenience.

Last time I checked, there are over 60 biotech companies on campus. I guess the number has increased by now. The Hong Kong Science Park has got into momentum and created an ecosystem of expertise in the respective focus areas. Interdisciplinary collaboration is possible. Needless to say, it is located within a short distance to your university. Having a university neighbor provides us another convenience in seeking expert advice and research collaboration. You should consider opening your business here in the Hong Kong Science Park too!

Al: Great, great! It looks like I don't have any reason not to do so now.

Pal: Going back to the beginning, since we are talking about business, there are several things you need to pay attention to. The way I see it, the cost of doing biotech business in Hong Kong can be higher than doing so in other places. Therefore, securing financial support is critical. Nevertheless, the cost may be justified by the convenience of access to investors and potential markets, the freedom of information and idea exchange, a low tax rate and a sound legal system that protects people's rights.

Besides cost calculation, you will need to have all risks assessed to make sure your business will not face heavy competition on one hand and have no market on the other. A clear business objective and marketing strategy are essential to the viability of your business. You may want to consult people with business

and marketing knowledge for advice. Just like writing a proposal for research grant application, a good execution and time management plan will help you see through the whole project and guide you to complete the different tasks in a timely manner.

For you Al, building a team of skilled R&D personnel would not be a problem because you have trained a lot of graduates who can tap in easily in your startup. In other cases, however, recruiting the right R&D personnel or skilled technical staff can be challenging. We somewhat started to face competition with others on staff recruitment in the market. This is perhaps a sign to show that we have more opportunities for graduates with life science background now. However, it may also indicate that we do not have enough personnel around with the level of technical skills we need. The short-term remedy may be to provide training to junior staff members so that they can take up more sophisticated tasks sooner, or to look for personnel from places outside Hong Kong. In the long run, we may need to form partnerships with academia to train interns in order to nourish technical specialists earlier.

Al: Indeed. I hope our life science students will see the changes now that they do have opportunities besides a career in academia. We surely need more graduates with a life science degree, and perhaps a higher degree in this discipline too. I guess we should teach entrepreneurship to science students as well.

Pal: Yes, I am hopeful that the tide will be turned when we have these difficulties taken care of. Although we may start high-tech industries later than other neighboring countries or regions, there is no reason we cannot catch up. The Government continues to offer more financial support to the development of high-tech industries in Hong Kong[6,7], with a goal to double the gross domestic expenditure on R&D in five years and to encourage investment in technological R&D from private sectors[7]. I believe they finally see the importance and benefits these industries can bring us and decided to act on it. In this regard, I wish they would extend their support further. In addition to fostering home-grown biotech entrepreneurs, they should consider attracting internationally-renowned biotech or pharmaceutical companies to open R&D centers in Hong Kong to create opportunities to the local ecosystem.

Meanwhile, the Hong Kong Science Park is expanding: another two purpose-built, R&D-fit office buildings are now under construction on campus. Another Innovation and Technology Park, which is an extension of the Hong Kong Science Park, is proposed to be installed next to the border facing Shenzhen city. The new park's undertakings will be focused on biomedicine, robotics, smart city and financial technology ("fintech"). Besides providing additional R&D infrastructure to local high-tech industries, the establishment of the new park is expected to foster collaboration and synergism between local high-tech business stakeholders and the alike in Shenzhen. This is another pointer showing the commitment of the Government to further strengthen our capacity in the development of high-tech industries. I am optimistic that we can generate successful examples here in Hong Kong. Certainly, we are working to make sure our company is among these successful examples too!

Al: Good luck to you, Pal! Let me know if you need my help anytime! Indeed, it is a waste if we cannot turn our knowledge into something useful and beneficial to people, especially when we are capable of doing so. I can feel that we have an opportunity here.

Pal: Thanks so much Al! Let's get a chance to visit Professor Sam. In fact, I do have some marketing questions that I would like to seek expert opinion. From what you mentioned earlier, I believe I can learn something from him.

Al: No problem. I can help arrange a meeting with him.

Pal: That would be marvelous! Thank you so much. Well, I guess it is time for lunch. Shall we?

Al: Certainly. Let's go!

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Chapter 9

BIOTECHNOLOGICAL READINESS FOR THE SAKE OF BIOSAFETY AND PUBLIC HEALTH

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Abstract

In 2003, a severe acute respiratory syndrome ("SARS") outbreak originating from mainland China paralyzed Hong Kong and thrust the city into the global health spotlight. The events that unfolded over the course of this deadly epidemic served as a wake-up call for both local and international public health professionals to ensure readiness in the face of future global pandemics. This chapter presents the story of how international air travel broke through national boundaries and assisted in the spread of disease in the SARS epidemic, and how genomics technology has evolved to combat pathogens including the SARS-coronavirus and Ebola virus. Finally, we discuss the rapid development of next-generation sequencing ("NGS") technology, its significance in biosafety and bio-surveillance, and the potential contributions of NGS technology to the economy in Hong Kong.

Dedication: The authors would like to dedicate this article to the heroes who fought so selflessly against the SARS outbreaks in 2003.

Why is Biotechnological Readiness Important?

In 2003, Hong Kong faced a sudden onslaught of deadly cases of SARS stemming from a then-unknown pathogen. In the midst of mounting uncertainties, Hong Kong's medical system was on the verge of collapse, and the World Health Organization ("WHO") swiftly declared an international travel recommendation to restrict the spread of disease, effectively placing the city under quarantine. The resultant economic losses and psychological impact of the SARS outbreak on Hong Kong's citizens—as well as on the global health community—have been far-reaching; indeed, the SARS outbreak dramatically demonstrated a need for improvements in global preparation and readiness in the face of unpredictable and deadly infectious disease outbreaks.

Newly developed biotechnologies in the field of genomics—and, in particular, gene sequencing technology—are particularly significant in furthering the global health community's ability to effectively detect and combat future disease outbreaks. We believe timely investments in biotechnology, particularly those targeted towards biosafety and bio-surveillance will position Hong Kong to become a leader in the genomics industry.

In the first section (Section 1, Infectious Diseases), we retrace the course of the SARS outbreaks from mainland China, and consider the role of international air travel through Hong Kong as a potential factor in the spread of future outbreaks. We additionally discuss the challenges involved in identifying and tracking the specific pathogen involved in the SARS outbreak, and why future outbreaks are inevitable. In the next section (Section 2, Technological Readiness), we discuss gene sequencing biotechnologies, and shed light on the promise of next-generation sequencing ("NGS"). In the final section (Section 3, Unique Benefits), we focus on addressing the significance of biotechnological readiness for biosafety and public health, both in Hong Kong and abroad.

1. Infectious Diseases: A Genuine Threat to Public Health

1.1 Overview of the 2003 SARS Outbreaks

The first known case of SARS occurred in Foshan, Guangdong Province in November 2002. New cases continued to emerge in other parts of mainland China and, by February 2003, over 300 cases were reported, with approximately one-third of the cases afflicting health care workers.[1] Infected individuals travelling from mainland China subsequently spread the pathogen to Hong Kong[2] and a number of other countries, including Canada.[3]

The rapid transmission of the disease can be modeled through the "super-spreader" phenomenon (Figure 1)[4]. The index patient of the Hong Kong epidemic was treated at Prince of Wales Hospital and was associated with at least 125 secondary cases.[5] Subsequent super-spreader events occurred at Hotel Metropole (13 cases) and the Amoy Gardens housing complex (over 180 cases) in Hong Kong and aboard an Air China flight traveling from Hong Kong to Beijing (22 cases).[6] The Hotel Metropole cases were responsible for the spread of SARS to Canada, Vietnam, and Singapore through international travel (Figure 1). The imported case to Canada resulted in 128 SARS cases at a Toronto hospital6 and thereafter resulted in a total of 438 suspected and probable cases, eventually claiming 44 lives in the Greater Toronto Area.[7]

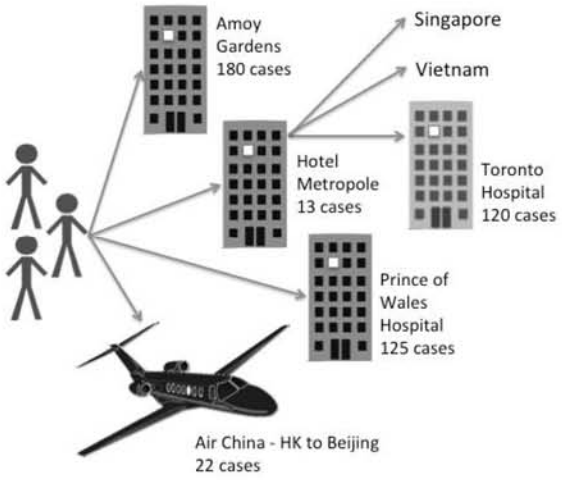

Figure 1 Super-spreader events in 2003 SARS outbreaks.

In March 2003, the WHO established a global network of research labs to identify the causative agent of SARS, and the SARS coronavirus ("SARS-CoV") was identified in early April; also the around-the-clock efforts resulted in the timely sharing of the pathogen's complete genome sequences information online by lead researchers—noticeably Professors Fredrick C. Leung of the University of Hong Kong and Dennis YM Lo of the Chinese University of Hong Kong and their colleagues.[8] After over 8,000 reported cases including 774 deaths in 27 countries,[9] the SARS pandemic ended in July 2003 as a result of successful infection control measures, including strict travel quarantine, rather than through traditional medical interventions. Over 80% of the deaths stemmed from mainland China and Hong Kong.[10]

1.2 The Difficulty of Containing Outbreaks

The historic race to contain the outbreaks was difficult for several reasons. First, the outbreaks were accelerated with typical rapid super-spreading. Second, at the time of the outbreak, the best available technologies to combat the outbreaks were centrally located in the research or government labs of a virtual international network, and were unavailable for on-site and real-time analysis. A thorough understanding of these difficulties is necessary in improving future approaches to disease outbreak prevention and control.

Early Actions Could Have Prevented Super-Spreading

When reacting to any disaster—whether natural or man-made—preparedness can oftentimes determine the success of the response. Sufficient preparation enables public health professionals to respond quickly and accurately, and can result in the difference between a simple, localized cluster of disease cases, or a full-blown global pandemic. Modern pandemics, including AIDS, Ebola, and Middle East Respiratory Syndrome ("MERS"), have occurred on a global scale due to the unfortunately efficient mode of transmission, and the occurrence of at least one super-spreading event. The four key factors in preventing and limiting the spread and sustained timeline of an outbreak are early discovery, early diagnostics, early intervention, and early quarantine. As such, our ability to minimize the infection of so-called "super-spreaders"—individuals positioned to rapidly and widely transmit the disease—is likely the difference between an infection cluster and a global outbreak.

The following case regarding two infected individuals traveling from Hotel Metropole

to Canada demonstrates the importance of early actions in preventing super-spreading. The first individual landed in Vancouver, Canada, and was taken to the hospital directly without exposure to local community, and was immediately isolated with quarantine and managed with top level of infection controls, as Vancouver hospital's infection control team was well-informed about the growing SARS epidemic in Southern China. As a result of these early actions, Vancouver was able to effectively control SARS exposure and infection.

The second infected individual flew home to the Greater Toronto Area, and was treated at a local hospital as a suspected tuberculosis case, without additional efforts to isolate and quarantine the patient. This unfortunate mishandling resulted in the numerous Toronto SARS cases. The difference of the outcomes of these two cities demonstrates the effectiveness of containment in the face of potential outbreaks, by staying informed and vigilant in global bio-surveillance. Additionally, this case indicates the significance of understanding and identifying probable super-spreader mechanisms, and the importance of future investment of resources in the development and placement of effective preventative measures.

Novel Pathogens Demand Innovative Measures

The determinants of an outbreak originate largely from our ability to effectively handle the many unknowns involved in complex cases of disease outbreak and management. In the case of the 2003 SARS outbreak, healthcare professionals worked tirelessly to contain the outbreak within healthcare systems that were inadequately prepared. There was no effective method of determining, with certainty, who was infected with SARS-CoV, and so widespread quarantines were ordered to prevent infection and spread, which in turn led to substantial damages to the economy and on the broader confidence of Hong Kong's citizens. Notably, similar damages happened in Toronto as well and "citizens were impressively calm and cooperative, notwithstanding innumerable disruptions to their working lives and quarantine requirements that affected thousands."[7]

Unfortunately, SARS remains a challenge to diagnose and manage because its symptoms resemble those of many other respiratory infections. The previously available molecular diagnostic tests for SARS-CoV are limited in their "reliability" and "sensitivity", and rapid identification and characterization of novel coronaviruses are difficult at best.[11] Moreover, due to a lack of portable and reliable detection systems, large numbers of patient samples collected at dispersed locations must be sent to centralized laboratories for rushed processing and analysis. Every transaction of a physical sample along this chain of events is an unfortunate, potential opportunity for human error; indeed, the most sensitive tools used to detect the virus—currently polymerase chain reaction ("PCR")—are also subject to chance contamination, hence a widespread need for better contamination controls of PCR-based amplifications of viral targets.[12]

The major difficulty of clinical detection of SARS results from symptom similarities of SARS infection to broad array of pathogens for other known respiratory dysfunctions, including both viral and bacterial infections. The most advanced biotechnological tool at the time of the 2003 outbreak was the "gene chip" (or microarray) technology, which allowed for massive parallel detection of small portions of all known genomes of respiratory pathogens, including subclasses of coronaviruses.[13] However, gene chips possess a critical limitation also common to the aforementioned PCR-based methods: gene sequences of pathogen "targets" must already be available to make precise "recognizing probes". Although confined by this limitation, scientists and biomedical researchers worked around the clock to develop timely and improved molecular diagnostics tools to quickly detect the newly isolated SARS-CoV, including "flow-through arrays" invented by Prof. Joseph Tam of the Hong Kong University,[14] and electrically accelerated gene chips by Prof. Albert Yu of the Hong Kong University of Science and Technology.[15]

1.3 Future Outbreaks

Certain viruses resembling SARS-CoV have since been identified in animal reservoirs, and these viruses have been shown to be capable of infecting human cells without any prior adaptation,[16] suggesting that SARS could re-emerge. With constantly increasing globalization, disturbances to local or global ecological environments are inevitable, and future disease outbreaks appear unavoidable (see Figure 2).

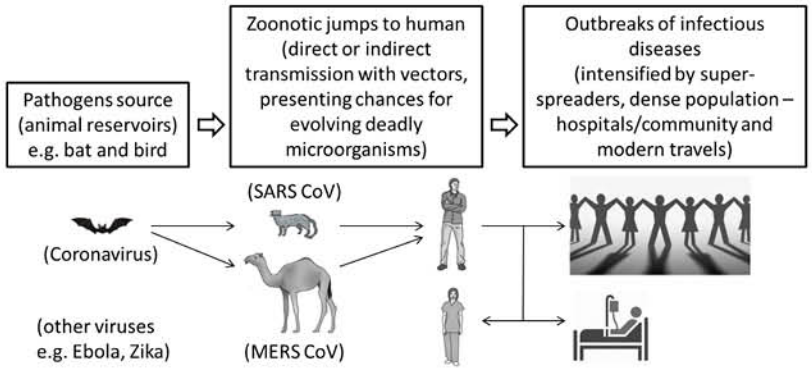

Figure 2 The emergence of recent coronavirus outbreaks.[4]

2. Technological Readiness

As discussed above, the goals of effective disease outbreak prevention are early discovery, early diagnostics, early intervention, and early quarantine. As the latter two points are the expert domains of epidemiologists and infection control specialists, we will restrict our discussion on the more technologically relevant former two keys, i.e. molecular diagnostics with real-time discovery capacities.

Scientists researching recent outbreaks have embraced newer generations of biotechnological tools—namely, next-generation sequencing ("NGS"), which allows for previously unobtainable throughput, speed, and turnaround times. However, the NGS technologies currently available would have not been able to eliminate the spectrum of technological difficulties present during the 2003 SARS outbreak, as discussed below.

Thermal imagers are widely used in airports (as well as other port-of-entries), as they provide quick detection of travelers with high fevers—a characteristic symptom of an active SARS or MERS infection. Thermal detection is not a robust screen though, as viral incubation and symptom onset times can range anywhere from 2 to 10 days.7 In response to the challenges encountered during the SARS outbreak in 2003, traditional PCR, microarrays, and NGS have all been employed during subsequent infectious disease outbreaks, including the recent Ebola pandemics.17 The excellent short review by Wong & Tang18 includes a historical perspective on the evolution of three generations of the sequencing technology. (See Box 1 for a summary of the latest developments in gene sequencing technologies by selected start-up companies.

2.1 Review of Sequencing Technologies

Currently centralized gene sequencing core facilities are the key customers at the upstream of the industry chain. Illumina, ThermoFisher and Roche account for 83.9%, 9.9% and 5.2%, respectively, of the total number of installed sequencing machines. The dominance in the sequencer market exerted by Illumina is a reflection of customer need, namely, accuracy and low per-base sequencing cost.

Although NGS technologies provide unprecedented throughput, they possess three essential, major limiting factors to wider use of current gene sequencing technologies:

1. Expensive Gene Sequencing Equipment: NGS technologies currently require large capital costs; the widely used Illumina HiSeq 3000/4000 are priced at over US$960K.

2. Barriers to Sequencing Data Analysis: Although there are specialized companies to provide bioinformatics and data analysis services, the complexity and technical difficulty of sequencing data analysis must be lowered to broaden the scope of applications for gene sequencing.

3. Gene Sequencing Turn-Around Time is Too Long: The typical "sample-to-answer" time requires several weeks. The current sequencing workflow also requires samples of high quality and quantity, expectations that are not realistic in many real-life circumstances. Most third-generation sequencing equipment developers are attempting to break away from these restrictions.

2.2 SONAS (SOlid-state NAnopore Sequencing): Core Technology Enables Portable and Field Uses

The value of portability and rapid diagnosis in a sequencing platform cannot be overemphasized. Portable sequencing platforms will enable upstream infection and disease prevention through simplified, effective bio-surveillance at a broad array of geographic locations where increased infection risk is a concern, including port-of-entries and agricultural centers; moreover, these platforms can inform healthcare decisions by providing relevant, up-to-date data at both the clinical and government level. Genvida has proposed the SONAS technology, which integrates knowledge and know-how from IT, IC and biotechnology. The end result is a real-time portable sequencing system (see **Figure 3**) that overcomes many of the key shortcomings faced by existing NGS technologies (see **Figure 4**).

Three key improvements of the nSeq sequencing platform over existing gene sequencing technologies are:

1. Simplified and Robust Workflows: The nSeq Biochip implementation, which integrates micro/nano fluidics, passive/active DNA translocation/guiding technology, and sequencing-by-direct-read or SBDR detection, can essentially render sequencing library preparation unnecessary. Moreover, the nSeq system does not require expensive, unstable reagents, which allows for faster, cheaper turnaround times, and increased sensitivity of detection with greater tolerance for so-called "low quality" or "insufficient quantity" samples that cannot be used in existing NGS technologies.

Figure 3 SONAS – SOlid-state NAnopore Sequencing technology

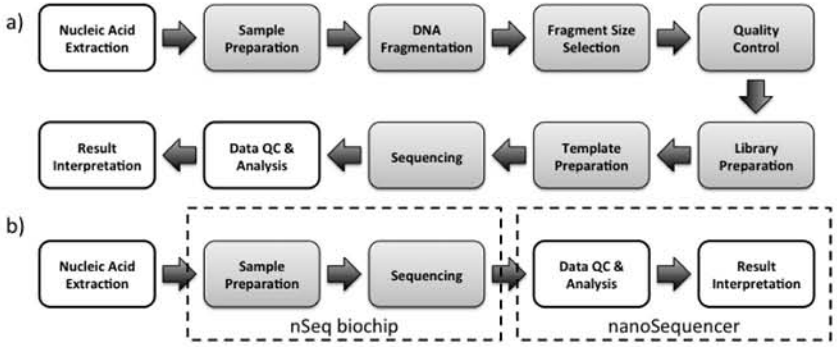

Figure 4 Comparison of the workflow for (a) the current NGS technologies, and (b) SONAS.

As detailed in Figure 4, the complex and labor-intensive sample preparation required by current NGS technologies will be replaced by a single injection step of the double stranded DNA ("dsDNA") into the nSeq biochip. Purified dsDNA molecules enter the nSeq biochip, pass through with electrophoretic progression via a microfluidic channel, and subsequently through a nanofluidic channel to enter the parallel-channels multi-nanopores layer. Regions of a single dsDNA molecule will then be dissociated sequentially to be threaded through the single solid-state nanopore. As the sample's nucleotides pass through the nanopore, the electrical sensing capability of our SONAS system will rapidly and accurately identify the bases and record in real-time (milliseconds per base) the actual base sequence by communicating the real-time signals to the signal processing unit on-chip, and using our proprietary SBDR method to decode and relay the results further to the operating and controlling "nano-Sequencer" unit.

2. Low Cost: The miniaturization of our sequencer is made possible by way of massive production scales with an engineering design unique to our SONAS technology. The nSeq BioChip utilizes physics-based SBDR to transfer the detection load to consumable chips with signal-processing functions, resulting in a sequencer that is lightweight, requires minimal workloads, and is ultra-cheap to manufacture. In addition, SONAS is crafted to be a robust system that requires little maintenance; it will possess a longer-than-usual usable lifetime and stable versioning, eliminating the need for constant upgrades and re-training for new protocols.

3. Low Bioinformatics Load: Existing "shotgun" and "short read" sequencing analysis schema require the reconstruction of a genome map, or alignment to an already-existing reference genome. Short reads of genetic sequences can make this process taxing, requiring long analysis times and extensive computational resources, including highly specialized expertise and high-performance computer clusters or parallel cloud servers. Genvida's platforms effectively solve this problem through:

    a Real-Time de novo Assembly, through an in-order sequential dissociation mechanism, and

    b Long "Read Length" and "Sequence Spans" to make in-line bioinformatics possible, thus eliminate the need for expensive and highly specialized off-line bioinformatics.

Ultimately, SONAS will provide comparable or increased per-base accuracy, and more flexible per-run capacity of high throughput with comparable or better sequencing cost-per-base than all existing sequencing systems.

3. Unique Benefits: Why Development in Hong Kong?

Historically, the development of any high-impact technology—such as smartphones and internet technologies—requires substantial upfront resources and concerted efforts from government, industry, and academic sectors, as well as support from the public. Moreover, successful development of high-impact technologies hinges critically on the niche environment present. Below, we evaluate the potential for biotechnology development in Hong Kong from two angles: first, to discuss how Hong Kong is presently poised to push forward and compete effectively in biotechnological development, and second, to discuss why Hong Kong is a uniquely suited venue for cutting-edge technological advancements.

Unquestionable Need for Better Preparedness

Hong Kong is a global, metropolitan city, well known for its extremely high population density of over 7 million people living on only a small area of 2,755 km^2. Annual passenger movement in 2016 through the Hong Kong International Airport exceeded 70 million,[19] with over 300,000 individuals crossing daily between China and Hong Kong.[20] Given Hong Kong's population density and massive population flow, the city is highly susceptible to pathogen attacks and spread of infectious diseases.

When we reflect on the challenges during the 2003 SARS outbreak, we must admit that Hong Kong was not adequately prepared and equipped to effectively combat an infectious disease outbreak. Over one month elapsed before scientists and laboratories across the globe were able to successfully isolate of the pathogen, and subsequently confirm the genetic sequence of SARS-CoV. Researchers were handicapped because of the marked lack of a reliable sequencing technology that was capable of reading and mapping the virus's genome sequence with a sufficiently quick turnaround time, and with enough portability and mobility for on-site diagnostics.

The SARS epidemic is a valuable lesson to all of us. Since 2003, there have been numerous efforts in developing diagnostic techniques and precautionary measures for future disease outbreaks. The past decade has seen enormous leaps in biotechnological development. In spite of these notable successes though, current technologies still face several crucial bottlenecks, and further research efforts in developing of improved sequencing technologies are essential. Undoubtedly, now is the right time for Hong Kong to build upon up-to-date achievements, and to explore and investigate more capable and powerful gene sequencing technologies.

Hong Kong Can Be The One-Stop Shop For Leading Biotechnology

In recent years, Hong Kong has witnessed an acceleration in high-tech development, coupled with strong support from the government, and enterprises and industry professionals have made "big strides in cementing Hong Kong as a biomedical technology hub, with its growing role as a springboard for mainland Chinese and international medical technology enterprises in taking on global markets." In the Hong Kong & Guangzhou International Conference on Stem Cell & Regenerative Medicine on December 16, 2016, Chief Executive Mr. Leung Chun-Ying, affirmed the Hong Kong government's strategy to invest in biotechnology development, emphasizing that "Hong Kong is taking bold steps to harness the vast potential of biomedical research, science and technology", and "the Government has put a priority on promoting innovation and technology development – including biotechnology."[22]

Hong Kong's growing emphasis on biotechnology is matched by the set-up of billion dollar-scale research and development funds, cementing Hong Kong as a forefront of innovation and technology. In 1999, the Innovation and Technology Commission (ITC) was established to facilitate and promote the advancement of Hong Kong's innovation and technology through the Innovation and Technology Fund (ITF) Scheme.[23] As of 2011, the ITC has already financed nearly 2,500 biotechnology-related research and

development projects since its establishment. As a result, Hong Kong has witnessed robust business growth of approximately 300 homegrown biotechnology companies, demonstrating the municipal government's dedication and support of biotechnology development.

Aside from government support, Hong Kong offers a robust legal and financial framework with attractive fund-raising sources—an environment highly conducive to cultivating cutting-edge biotechnology startups and aggressive growth for industry leaders.

As remarked by Mrs. Fanny Law, a Board Member and Chairperson designate of Hong Kong Science Parks Corporation, Hong Kong possesses several unique advantages essential to the effective development of a biotechnology industry: [24]

1. The availability of internationally-recognized drug testing and approval facilities

2. The presence of acclaimed academia and research experts in the life sciences

3. The provision of superb infrastructures essential to the realization of biotechnology ideas, from conception to commercialization

Moreover, Hong Kong possesses a distinct geographical advantage. Situated at the entrance of Pearl River Delta and adjacent to Shenzhen, a major city regarded for its rapid emergence in high-tech industries in recent years, Hong Kong is poised to leverage the unique opportunities, support, and resources available within the region. As a bridge between mainland China and international markets, Hong Kong offers an unparalleled opportunity for local enterprises to explore one of the world's fastest-growing healthcare markets—China—all the while enhancing its technical competencies by gaining the rich human resources and research strengths in return.

We are now in a decisive moment to fulfill Hong Kong's long-time aspirations to transform the city into a knowledge-based economy and a world-class innovation center. The timely development of a biotechnology sector will not only improve public health, but will also thrust Hong Kong into the global center of high-tech and economic development for the coming years.

4. Concluding Remarks

The 2003 SARS outbreak serves as a sobering reminder of the very real possibility of disease outbreaks and epidemics. Advancements in genomic sciences and point-of-care technologies will ensure biotechnological readiness to achieve improvements in public health.

We believe that up-and-coming biotechnologies present promising medium- and long-term investments, and can bring about significant, positive financial impacts to Hong Kong, as the global sequencing market has already experienced exponential growth. There currently exist several multi-billion-dollar government initiatives in different countries, including the Human Genome Project (USA),[25] the100,000 Genomes Project (UK),[26] and the Precision Medicine Initiative (USA and China),[27] to promote wider use of gene sequencing technologies in science and medical research. Simultaneously, patient demand for gene sequencing technology across a number of medical disciplines is rapidly expanding, including non-invasive pre-natal testing and cancer patient monitoring. Indeed, there are numerous medical and non-medical applications to gene sequencing (see **Figure 5** and **Box 2**). Moreover, according to a report by Forbes, the global market size is expected to expand to over US$100 billion by 2035 with a CAGR of 17% (see Figure 6). [28]

Mr. Tung Chee-Hwa, the first Chief Executive of Hong Kong, hoped to promote and develop the city's high-tech industry, with an end goal of reducing financial dependency on real estate and finance. After two decades, the advancement of Hong Kong's industry still lags behind the other three "little dragons of Asia", Singapore, Taiwan and South Korea. Mr. Leung Chun-Ying, the current Chief Executive of Hong Kong, has doubled down on high-tech opportunities by allocating resources in support of entrepreneurs hoping to start new businesses in Hong Kong.

Today, Hong Kong is at a watershed moment in her history. With the One-belt, One-road Initiative proposed by the central Chinese government, Hong Kong has been granted a second opportunity to launch herself into the high-tech industry. The combination of IT/IC and biotechnology will put Hong Kong onto the global roadmap of technological innovation and development. We have the know-how and vision necessary to realize the SONAS sequencing technology, whose market potential exceeds US$100 billion. The success of SONAS will lift up the industrial infrastructure in Hong Kong, the Pearl Delta Region and China, benefitting a myriad of other industries, and will—perhaps most importantly—hopefully inspire the next generation of young Hong Kong

innovators to seek out their own futures.

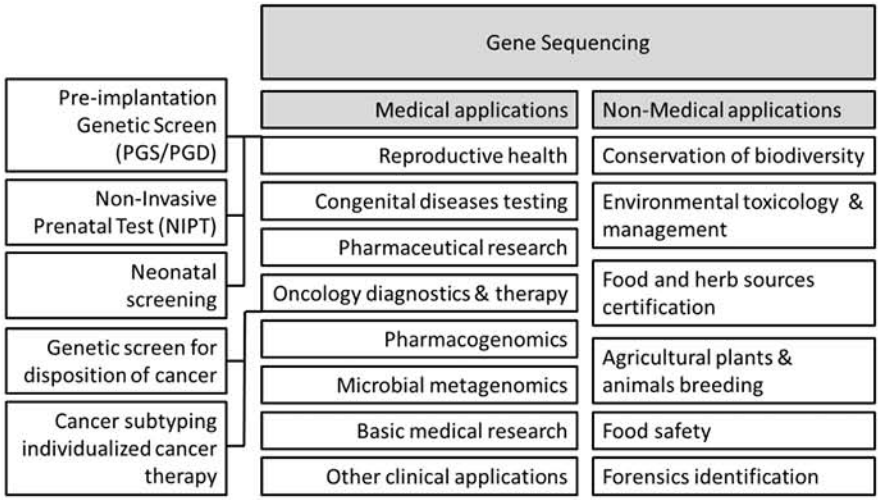

Figure 5 Main applications for gene sequencing.

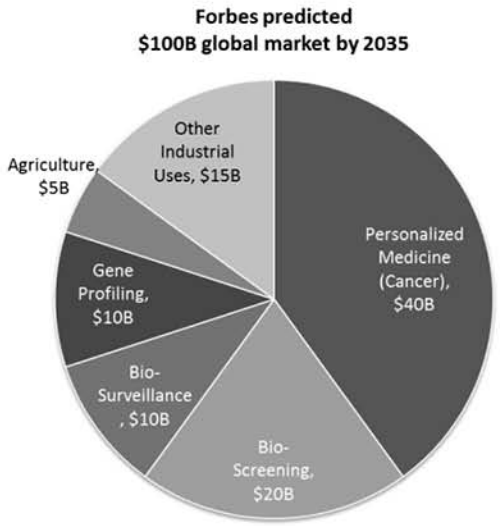

Figure 6 Potential market size estimated according to Forbes.

Box 1. Current Attempts to Overcome Bottlenecks of Existing NGS Sequencing Technologies

The skewed distribution of sequencers to small numbers of sequencing centers is in part caused by the design and constraints of the currently dominant Illumina systems—that is, the existing systems require complicated workflows, large numbers of highly trained staff, and expensive reagents. Several startups are developing technologies to overcome these shortcomings. 10X Genomics and GnuBio are developing their respective sample handling microfluidic chip technologies to simplify the workflow and sample preparation. The prepared DNA samples are then analyzed using existing sequencers, such as Illumina systems.

Pacific Biosciences and Oxford Nanopore Technologies are the major third-generation sequencing technology companies that enable long read lengths in a single read. The Pacific Biosciences single-molecule, real-time technology is based on specific enzymes and nanophotonic visualization chambers.

Oxford Nanopore Technologies utilizes sequencing by indirect read ("SBIR") to measure the characteristic changes in membrane current flow induced by the natural nucleotides passing through a protein nanopore. Different concepts are under development to improve SBIR performance. Genia Technology measures the characteristic changes in membrane current flow induced by specific tags that are guided through a protein nanopore. These tags, previously attached to individual nucleosides, are then released in sequential order upon their incorporation into a new strand of DNA according to the template. Stratos Genomics measures the characteristic changes in membrane current flow induced by a synthetic DNA strand that passes through a protein nanopore. This synthetic DNA strand is made of expandable nucleotides (X-NTPs) and generated when a surrogate complementary strand is synthesized.

The aforementioned second and third-generation sequencing technologies are essentially "sequencing-by-synthesis," with some variations in the detection technology or in the sample preparation. At this stage, both generations of technology coexist, due in large part to low accuracy and poor throughput of existing third-generation technologies. The scope of use of third-generation technologies is still relatively small. Second-generation sequencing is capable of higher throughput and higher accuracy, and so it remains the mainstream technology used in gene sequencing.

Box 2. A Critical Application of Sequencing Technology: Combating Antimicrobial Resistance

Antimicrobial resistance ("AR") in agriculture and among the general public presents itself a major challenge to infection control. New approaches to this problem utilize short, artificially-created RNA sequences that target and destroy unwanted genomes, such as those of newly-evolved AR strains of microbes.[29] This biotechnology is based on the groundbreaking discovery of the CRISPR/cas9 system, which allows for remarkably effective "genome editing."[30] To effectively design the RNA sequences used to kill unwanted microbes, precise, massive, and scalable sequencing technologies are necessary to effectively detect and determine the optimal RNA guides. A robust, sensitive, and fast gene sequencing platform like SONAS would enable effective research for CRISPR/cas9-based infection control measures of antimicrobial resistant pathogens.

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Chapter 10

OPPORTUNITIES AND CHALLENGES FOR MEDICAL THIRD-PARTY TESTING CENTERS IN CHINA

医学第三方检测中心在中国的机遇和挑

Sherman Zheng

郑勋华博士

Overview

In recent years, strengthening medical third-party inspection is a major policy development in the healthcare industry in China and also an integral part of the structure of the national health care reform. According to factual data gathered on China's medical system and the healthcare related industries, this report provides a preliminary market analysis, competition analysis and industry product segmentation. It also highlights real problems and challenges facing professionals and entrepreneurs who are in the trenches trying to effect change. Lastly, some ideas and proposals filtered through the author's personal experience are put forth for the readers' consideration.

概要

加强医学第三方检测是近期中国大健康产业发展的一个政策，也是国家医疗结构改革的一个组成部分。本文根据国内近期医疗系统和医疗卫生相关产业各方面的实际情况，谈了一些初步的市场分析、竞争对手、医疗卫生产业定位等形势。也道出现实工作和运作中遇到的问题和挑战，同时提出了本人一些前瞻性的想法和提议。

一、 前言

近年来，一轮基因科技的新浪潮正在兴起，而基因检测领域受到国家政策不断推動，暖风频吹。在此新浪潮中，我们理应踏着滑板，成为弄潮儿，并紧跟时代的航船不失时机地向前跟進。我们成立的第三方检验中心，正是应该成为新浪潮中搏击的桥头堡，促使我们进入大陆市场成为排头兵。而要让第三方检验中心真正发挥这些基本作用，我们需要大量的前期投资才能做到。我们将从国内市场、竞争对手、公司定位以及面对未来的挑戰和随时出现的新机遇等几个方面来提供实际情况以供借鑑。

二、市场分析

市场的形成有其自身内部发展的原因，当然也离不开大众的需要，也离不开对于新技术的运用，以及政府顺着市场方向的推动力。第三方检验机构的兴起正是在这种大的背景下起步的。国内既有原有的检测机构转型而成的第三方检验机构，也有近几年成立或上市的第三方检验机构。我们不能期望中国回到二十年前，象"金域"或"达安"在独家创业时的环境，那时的检测机构是可以属于低投资高收益。现在我们已是面临国内更为激烈的竞争环境。不过，市场永远都充满了机会，关键在于我们能不能在合适的时机抓住可能的机会，加重投入，及时纠错，快速推进。

我们要清晰看到這些年来不少公司在国内投资所遇到的挫折，既有人为的因素，也不能排除有市场的因素。我们需要好好总结内在的原因，是我们不了解国内市场，过于冒进，还是没有找到合适的销售渠道以及营销专才，都要详细加以分析，以便对症下药。如今的国内第三方检测市场，实际上已经完全进入了红海竞争阶段。比如说国内的第三方检测老大的金域，目前的资本报酬率（即ROE）也只有6—8%左右。也就是说，如果我们也还是参照金域集团所在的市场领域，按照6%的资本回报率来

算的话，以我们投资在广州3000万元人民币来计算，我们要整整16.6年才能回本，如用复利来计算也要12年。這样的回报显然不能令人满意。因此，我们未来的重点市场领域显然已经变成惨烈竞争态势的检测市场。我们需要去寻找可能的新的蓝海市场，即我们要找到能充分体现公司的竞争优势，同时又还没有多少竞争对手开拓的市场。近几年趋势可能给了我们一些的机会，主要表现在以下几个方面：

(1) 2013年国家卫计委研究中心主任李青表示，我国对健康筛查体检，重大疾病的预警与诊断的需求不断上升，我国分子诊断行业面临新的发展机遇。2014年开始，全球体外诊断市场增加503亿美元，而中国所占只有35亿美元。考虑到中国巨大的人口基数，中国体外诊断市场将充满机会。而在其中分子诊断的表现最为突出。分子诊断市场预期复合增长率可达11%，占各类之首。随精准医疗，个性化治疗的兴起，分子诊断技术及相关产品也会相应的增加。

(2) 基因检测可预测疾病风险，对乳腺癌、卵巢癌、前列腺癌、结直肠癌、鼻咽癌、胰腺癌等10种癌症的94个易成基因的检测将有助于早期发现这些癌症。还有对先天性耳聋、青光眼患病风险的预测、对唐氏综合征、脆性X综合症基因检测， 甚至心脑血管病都可以通过基因检测来提前预测，基因检测市场正在兴起。

(3) 由于我国每年新发60－70万肺癌病人，占了全球的1/3。目前靶向治疗正成为临床治疗的主要手段，多项临床研究表明绝大多数EGFR基因突变阳性病人使用了靶向治疗效果显著。截至2014年底我国EGFR基因突变检测率只有约27%，对比日本、韩国、和香港台湾均超过80%的检测率，差距很大，也意味着机会也很多。现在“肺癌规范化诊疗万里行”项目在广州正式启动。去年8月份开始全国28个城市都要全面推广EGFR的肺癌检测。這对于我们已有成熟经验的公司来说就是很好的机会。

(4) 从2015年开始，国务院连续发出四道“金牌”：(a).2015年6月对西部地点鼓励类产业，对全部12个省、区、市都提及鼓励新增医疗机构。(b).2015年6月8日发布《国家发展改革委关于实施新兴产业重大工程通知》，将在3年时间内建设30个基因检测应用示范中心，快速推进基因技术大规模筛查的应用。(C).国务院2015年32号文件（6月11日）其中提议“放宽外商投资准入”、“鼓励外资开展创业投资业务”、“进一步放宽外籍高端人才来华创业，办理签证，永久居留证”、“大力发展第三方专业服务……检验，检测等第三方专业化服务”。(d). 6月18日，国务院办公厅印发《关于促进社会办医，加速发展的若干政策措施》，“政策红利”将鼓励医疗服务行业，包括医学检验机构和私人医生诊所开放。这一个个政府的扶持与鼓励政策的出台，将给我们新兴的企业和国内同行有了同一起跑的机会，也是切中了我们新公司在分子检验上的技术优势，使我们过去某些前進中的挫折反而可以成为新形势下的動力。让我们比其它人更迫切地加快步伐，将我们现有的资源重新布局。

(5) 在精准医疗方面，我们也可以抓住不少新的机会。精准医疗是一个近年比较引起重视的概念，是建立在了解个体基因、环境、以及生活方式基础上新兴的疾病治疗和预防方法。换言之，就是根据每个病人的个人特征，量体裁衣式地制定个性化治疗方案。“要在正确的时间，给正确的人以正确的治疗，而且要次次如此。”美国奥巴馬总统在2015年1月20日在国会的讲话中呼吁美国要增加医学研究经费，提议2016年向该计划投入2.15亿美元，以推动个性化医疗的发展。1月30日他又说：“投入人类基因组计划的每1美元的回报是140美元。” 他还说：“這一创新已得到巨大的经济回报，为這一创新鼓掌绝对没有错。”美国基因测序龙头股Illumina 的成長正是对于基因测序未来前景的回应。而2016年2月中国卫计委召集全国19位顶级专家组成了精准医疗战略专家委员会，並在3月11日在科技部召开首次会议，决定在2030年前政府将在精准医疗领域投入600亿人民币（相当于近100 亿美元）。中国的学者认为精准医疗的本质是通过基因组、蛋白质组等技术和医疗前沿技术，对大样本人群与特定疾病类型進行生物标记物的分析与鉴定、验证与应用，去精确寻找到疾病的原因和治疗的靶点，并对這种疾病不同状态和过程進行精确分类，最终实现对疾病和特定患者進行个性化治疗的目的，提高疾病诊治与预防的效果。而如果我们定位在分子和基因的检测公司，无疑能在精准医疗当中分享巨大的蛋糕。既然要精准，就首先要准确筛查出癌症，第二步用這个筛查出来的样品作進一步DNA序列分析，来确定這个突变片断的特性和分型。所以成功与否，还是在分子的检测水平上。未来新兴的公司将在此领域大有用武之地。在美国国會上，奥巴馬把DNA双螺旋结构的模型也放在身旁，摆出科学家的姿

态宣佈精准医疗。可惜只投入了2.15亿美元，为政治家买个冲锋号罢了。中国倒是动了真格，今后一定會有更多政府支持行为，精准医疗将是千載难逢的商机，我们要不失时机去捉住并紧紧不放。

(6) 国家卫计委2016年7月20日发出的37号文件指明医学检验室属于单独设置医疗机构，为独立之法人单位，並制定一系列的设置标准。這个法規将对医院和第三方检验中心都产生很大的影响，值得关注。总之，无论在分子检测、基因检测，还是在精准医疗市场都还有巨大的成长空间，这个市场规模足够大，加之各国政府，特别是中国政府在这方面许诺投以重金，可以说第三方检测的春天才刚刚开始。我们理应紧跟此潮流，发挥自身优势，加快医学第三方检验中心的投资与建设。

三、竞争对手分析

中国大陆经过30多年的改革开放，各行各业的市场都逐步从盲目打价格竞争走向成熟局部市场开战术。現時全世界的投资者都带着碰运气"闯关东"的心态来到中国赌一把。而中国的市场竞争也变得异常剧烈，局外人常常是不容易理解和看得透的。笔者曾到了一些偏远外省地方，也碰到数家省外的第三方实验的业务人员游走在周边县一级地区進行收集样品送回大本营作检测。再通过互联网报送结果。两地可相距一、二千公里之遥。這样模式发展也挺快的。另外作为发达中国南方广东医学检测为例，广州地区集中了中国大大小小十多间不同层次的第三方实验室，例如有目前中国规模最大的第三方验测公司，金域检验集团公司（1994年成立，以广州医学院为背景，已有8000员工，年产值三十亿人民币)。达安基因股份有限公司（1988年创建，以中山医科大学为背景)，近年已经和中国高新投资集团公司合併，是中国国内生产感染性病原菌和一些肿瘤相关分子诊断试剂盒的国内老大，現在已逐步转型向大型测试仪器的生产方面发展。还有以南方医院为背景的华银医学检验中心。在深圳则有以分子基因测序为主体的华大基因。外来杭州方面公司有艾迪康医学检验中心，及已上市的迪安医学检验中心。加上个别专科或特殊的第三方实验室如同雨后的春笋，有数十多间公司了。

值得注意的是，作为医院本身的检验室都是医院财源的一个重要部分，和影像检验室都是财政收入的支柱。检验室相当一部分的仪器都主要是進口的，而這些外来公司以自动化仪器作为免费投放，以卖该仪器专用药盒试剂为挣钱方式，很多项目的检测都可以通过该公司对有大专以上的人员作短期培训，就成为可以操作的技术人员了。所以此行业的门槛实际上还是不太高，只要有病源样品来源，就有大公司乐意上门投放免费的机器，医院也挣了钱，第三方实验室就只能从各方面去收取样品，从数量中取得薄利。而从医生的角度看，单单看检验单的数据，失去对检验本质的了解和综合分析能力，诊断有时会出现偏差，带来对病症的误判，至今中外医学方面的误诊率一直都存在，因此如何提高检验单数据的分析能力，也要能为病患者作好对结果的解释能力，两者都是第三方检验中心需要具备的基本素质要求。

至2015年，广州市正式被定为三甲医院一共有55家，即便是二甲医院，大部分低端检验，只要有一点条件，都会在自己医院进行。美国医院里人工的成本高，加上大量的私人诊所存在，而且检测的价格是市场浮动，第三方实验室的需求就大得多。看起来，現在国内比美国很多的大城市的同类实验室，竞争的环境还要激烈。还有一个问题，国内医疗检测项目价格，所使用试剂、仪器的应用都要统一上报国家食品药品监督管理总局(CFDA) 审批，每一项新上报最快的流程都要12-15个月，费用少则几十万，多则过百万元人民币。美国也比较严格，公司产品一律经由美国FDA审批，但实验室检测权限在各地州、市，联邦更多是交由平级技术人员交叉评估。就药品和试剂仪器而言，美国是全世界管理最为严格的了，由于美国各大医院、医学院的基础医学的根底强，基础的学问很深，使某些新的病种，新的检测项目可以得到一定的支持，上级管理机构也不会管得太死，可以开展一些新的独立的检测项目，特别在自己医院内部進行，這里就不多作比較了。

下面我们再以金域为例来具体说明我们这个行业的状况。金域1994年成立于广州，是我国目前综合实力最强、市场占有率最高、最大的第三方检验公司，在全国23个省会拥有省级中心实验室，每天为全国30个省的1600多家医疗机构提供医学检验外包服务，复盖全国90%地区，80%的检验报告可以24小时内发出。全公司2012年收入首破十亿人民币，2014年底已经突破二十亿。但他们真正强在病理方面，全国共网罗了70多位知名专家加盟作为技术支柱，具体建有实验室分点（估计主要是病理方面）：如肇庆、海南、上海、石家庄、太原、香港、南宁、長沙、成都、杭州、沈阳、吉林、贵阳、天津、郑州、重庆、昆明、济南、南京、西安、

合肥。在全国不同的地区和城市运作，亦为金域的知名度打造帝国。

在目前检测的项目中，以个人能力优劣为主的病理医生是在检测中最容易被分出技术高低的，看片的X光医生则是其次。而用自动化仪器来测试的项目，不同公司的仪器也会出现差别，但差别一般不会太大，毕竟都要CFDA审批通过。当然要用人工操作的分子生物学实验的结果则更会出现差别了。据南方周末报道，现在病理方面，全国有执照病理医生仅有九千余人，但真正需要的是10万名左右，缺口高达9万，而且好的病理医生准确率达90%，初出道的已经有正式执照的病理医生如没有上级医生指导，准确率也仅是26%-40%，所以好的病理专家价值很高，这也是金域集团可以在国内相当的一段时间里能巩固发展之本。也是他们的很大一个优势。结合以上广州的实际情况以及竞争对手的情况，现在广州起步发展第三方检验中心是一件很不容易的事情，面临周围强大的对手，我们一定要有超常的公司定位和战略战术，才能做到异軍突起。

值得关注的以清华大学、中国医学科学院等科研单位为技术依托的博奥生物公司，他们致力于为集成医疗（包括预测、预防和个体化医疗）领域开发和提供创新性产品和服务，研制开发出了生物芯片（包括基因、蛋白、细胞芯片和芯片实验室等）及相关仪器设备、试剂耗材。公司2000年成立，注册资产为3.765亿元，拥有24,000平方米的研发、生产和运营设施，其中包括临床诊断级微阵列芯片和配套试剂GMP生产车间，硅基、塑料基微流体芯片微加工洁净车间。博奥生物的飞速发展受到了各方的广泛关注。2002年，博奥生物作为亚洲唯一入选的公司，被美国《财富》杂志评为2002年度"全球最有发展前景的生物技术公司"；2003年国务院发展研究中心主办的《新经济导刊》杂志指出博奥生物公司是一个具有自主研发能力，并能够研制生产出可以转化的高新科技产品的企业。象他有自己专利产品的生物公司在国内並不多，值得提倡。

四、公司定位

在广州，第三方医学检测公司开发早、密度大，因此新公司的方向和定位就一定要有自己的特点，有市场的竞争力。这样我们的起点绝对不低于国内任何的同类公司，反而应该立足在高点之上的。在技术上我们可能还有一定的优势，但是我们不要忘了在商业上，关键在市场，在国内市场上如果我们把产品都定在相同跑道上去追、去挤已经跑了十多廿年的同行，除非他们所有人都是龟和兔赛跑中睡觉的兔子，可惜大家都有点象狼，我们不吃、不喝也难于达到我们的目标的。所以如果再把公司定位在常规的第三方检测公司则我们的劣势是明显的。因此，我们定位应在高端的分子水平上，放在分子病理和分子基因的层面上和当今人类对疾病的精准治疗、预警性的检测捆绑在一起。有了我们高端的起跑点，就没有必要和众多的竞跑者挤在同一跑道上，這才是扬長避短。具体的战略上，我们还可以考虑采用"农村包围城市"的基本战略。农村包围城市是中国共产党取得胜利的法宝。我们借喻到公司的发展是要把城市和农村的概念理清楚。其中"城市"除了在地域上是指一线大城市的含意，也包括技术上的层面达到生物最深的分子层次。那么所谓的"农村"在地域上是指远离了发展快的沿海地区，处在中国广大的中西部十二个省市和中国三、四线区县城市，而检测技术上则是指还停留在人体细胞、亚细胞的次级水平上。這也占当今中国20%一30%的人口（相当整整一个美国)。分子基因诊断必须有一定经济能力和文化知识的支撑。国内卫生行政部门在相当一段时间里把分子和基因检测的门槛定得太高，不管过去的原因如何，今后一定逐步发展一些适合基层开展分子检测的仪器或方法。面对這个有着二、三亿人口的"农村"，应有广阔的市场空间推广应用，肯定能大有可为，會双赢而造福于民。

五、現实工作所遇到的问题和挑戰

(1)　在中国，药品和人体医疗相关产业是严格受到政府和行政部门的监管，企业对收费的上线是没有定价的自由，每项检测的收费都要由国家制定标准，有收费编碼，并不存在自由竞争和市场导向。這里值提出的是，同一项的检测有不同检测试剂来源，成本是有不少的差别，特别是進口产品和国内的产品。

(2)　国内使用的检测的仪器都比較相同，所有的仪器，试剂和药箱都要CFDA批报，而大部分仪器也只认本公司的试剂和药箱(這是利润的大头)，也是公司挣钱主要手段。外国的公司剩余利益给了国内的医院或第三方实验室。任由你们打价格戰和竞争。這样谁手中有病人和检测的样品谁就占有剩余利润的市场。

(3)　作为医疗上能够发正式报告的检测机构，国家都有一套严格的标准。科室分有：临床血液与体液专业、临床化学检验专业、临床免疫检验

专业、临床微生物检验、临床分子遗传学专业和临床病理专业。总体要有至少1名副高以上的临床执业医師。每个专业至少有5名以上的医学检验专业卫生技术人员，其中1名副高以上，2名中级以上专业职称资格的技术员。设立1个专业的建筑面积不少于500平方米，每增加1个专业要增加300平方米。另外对电力供应、空调、废物暫存、污水排放、生物安全存放、疗医文档管理都有严格的规范管理，每年各上级省市部门都直接下到各实验室严格检查，发出年审合格証，门槛相当高，任何部门都是惹不起的。

(4)　目前，在中国国内所有人体的检测方法，使用的仪器，試剂的应用都要经过本国CFDA的审批，报请批文。流程大约要1年半至2年，费用约需人民币1百万至1百50万元左右。即使有了美国FDA，欧盟CE的认証也不例外。目前，在分子生物学方面，欧美的技术比中国要先進，精准度要高和稳定性强。這些公司多数采取把仪器投放在有检测样品的实验里，他们宁可免费提供机器和訓练技术员，但要买他们的试剂，這是赢利的大头。因为中国检测的訂价是封顶的，他买出了试剂合后，已取得了市场上最优厚的利益后，剩下的利润只有中国人之间通过控制样品来源或通过价格戰作竞争的手段，這种市场开发实际是不容易。

(5)　投资市场对生物科技的估计和预测:　可以讲国内外在经济报表、金融投资分析及预测都把生物科技产业和互联网列为本世纪最为引人注目的朝阳产业。特别是国内经历改革开放卅多年的高速发展，房地产和外来加工业所挣下的第一桶金都在找寻新的投资方向，自然有不少的目光是落在生物科技、健康产业的发展上。在這些产业中，人类生命中的"生、老、病、死"尤为重要。上世纪末，由美国起動了人类健康的登月計划，花了上百个亿美元起動了人类全基因的測序，並在本世纪初完满地完成了。在這个基礎上认识到精准医疗对解决人体健康，特别是癌症医治上的重要性、必要性和可行性。　当某些由基因的方面所引起的细胞的癌变，是要在分子基因的层面得到诊断，才能使用针对性的靶向药物(特别是生物药)進行准确指导性给药，才能达到精准治疗的效果。

当然，精准医学(Precision　Medicine)這是在多种领域高度集中成的新医疗体系，包括了人体分子基因的測序技术、个体基因与大数据信息科学的分析、个性化治疗走向临床的应用、组学与疾病和养生与环境的关联等等。而只把精准医学简单看成主要在基因測序和靶向治疗都是不够全面。通过測序，現在我们对人类基因的信息只是读懂了其中的3%，而有97%是还未解读的暗信息。是否我们可以理解成，在当前DNA測序所提供的数据还缺失90%信息作支撐，当然這些主要都是所谓暗信息，里面还有很多我们还缺失的測试信息。很多未解之迷。我们要紧密和临床相结合起来，要创建起寻找来自自非编码物质信息的检测方法和手段。所以要做到真正的精准，摆在我们面前的挑戰又是多么的巨大！机遇难道不是也伴随在其中嗎！

(6)　人体健康的各种相关的筛查检测是一个弹性很大的市场。当中包括产前无创性的检测，妇女健康例如HPV，嬰幼儿童的各类体检(有关过敏、耳聋等)，无创性癌肿早期筛检，癌肿个性化的追踪和监控肿瘤的演化，药物靶点的動态检测和治疗方案的设定等都将精准治疗作为一个大的服务性平台。目前也有不少商业机构拓展开发"天赋基因"检测的项目，其发展的前景並不明朗，有待观察。

(7)　今后检测方法的发展和癌症斗争会有相当密切的关系，特别是肿瘤患者相关的靶向治疗。基因检测能明确是否存在靶向治疗的靶点。但我们也要清楚了解到某些实际的情况，例如乳腺癌靶向治疗，药物主要有表皮生长因子受体(HER2)一血管内皮生长因子和以血管内皮生長因子(VEGF)为靶点的药物，二者均为受体的单克隆抗体，HER2阳性的乳腺癌，仅占乳腺癌患者的20%到－30%。即使这样，也还有一定的局限性，如靶毒副作用，耐药性(结合力不強，容易脱靶)，高昂的费用。加上靶向治疗的知识更新得特别快，信息量特别大，对于患者来说找到专业的医生进行咨询多方面的了解，才能给患者带来真正的好的疗效。检测的工作才能扎实、持久的铺开发展。

(8)　传统的中医无疑是老祖宗为我们留下来有关精准医学的一大宝庫，因为中医本身就是精准医学里某些方面的老祖宗。哲理上的个性化诊断，用药的个性化和精准度却往往停在经验主义的个人判断上，就象在一黑箱作业。在中医中药里如何发掘出能有科学性的大数据呢？具体地讲如何作出能有数据量化的检测呢？在未找到直接可测的方法前，是否可考虑利用目前临床患病者表观上出現的一些相对应的体征变量来作为参数，从而发展出新的检测数据呢？這都具有很大的挑戰性。

(9)　一带一路，是我国全新的发展方略。在陸路，是中西方两极的通道。中国在30多年，从落后封闭的地区发展到最好、最有活力的经济发展

区。中国西向连接了不同层次的发展中的国家，直到欧洲的发达国家。由于短期内我们经历不同的时期的生产模式和不断创新的各种产品都可以从这些中心地带找到互相需求的群体，并和這些广阔的第三世界分享我们前进中的一点一滴，增加国家柔性外交的软实力。为各个层次市场带来商业全方位的发展，把中国中医几千年优秀的传统产品，和改革开放30多年来的健康产业带出国门，真正做到厚德载物。值得我们高度的关注，在有条件的情况下搭上国家大方略的列車上。

(10)　香港和澳门作为行政特区，对广东在经济上起着非常重要的地位，但在科技的发展上，还有待起着更大的桥樑作用。香港有着国际一流的大学，大学的教师人才都是来自美英的名牌大学的精英，有丰富的国际资源，和学生的资源。历来香港的国际金融市场和国际商品的转口业务都是世界上令人仰慕的经济金鸡蛋和东方明珠，但這个金鸡蛋並不是由高科技所衍生，还没有高科技的实业产品扶持。在港的相当大部分的阶层及教育界期望学生输送往美欧名校去深造，或学成留在香港能進入精英阶层，可以保持高尚的平稳生活。香港多年出了不少成功的学术英才，当然近年来出类拔萃的是香港中文大学分子生物学家卢煜明教授，他开创出无创产前检测技术，已赢得世人的注目。這是一项很了不起的成就，有很高的科学和实用价值。香港行政区完全可以借助這个有突破性的势头，通过政府鼎力相助，也利用香港有丰富的资金来源，打造好相关的大平台，把這个本土产业链做大做强。

随着本世纪科学的進展，在新的科技上全世界已经把目光集中到: a.人工智能 ； b.能源； c.生物科技； d.互联网這四个方面里。其实以香港的基礎实力和地缘环境，完全可以有机会在其中的大健康产业和人工智能這两大高科技结合点上，打造出新天地，是有机会成为世界一大亮点。

香港已超过日本成为全世界人均寿命最長寿的地区，其中是值得思考和研究的: 在人类大健康的相关諸多長寿条件中，香港人的生活节奏紧，压力也大，平均居住的条件並不算好，而且生活在接近热带的地区，并且也还远未超越北欧发达国家(例如瑞士、瑞典、挪威)的人均收入、生活环境及社会的医保福利。是什么因素能使香港佔有了長寿福祉呢？其中人们是否可以联想到香港是非常熟悉中、西方生活方式，有着中、西方文化人文的交融，对中、西医的认可程度也有相当高的社会基礎。他们都可以从各个角度作充份比较，也能从這个最具多元化的社会里作出适合自己的多种自由选择。因而可产生更多维的思考模式和可以提供更多方面的数据，這也是可为人工智能提供更全面而有价值的信息。加上香港有最方便的進出口条件，其中包括各种相关的生物制品、药品和世界各地的仪器、配件等。自然也为多姿多采的人性化的人工智能产品提供了社会环境的氛围。

這里不妨谈谈人类不久将开始与人工智能机器人并肩工作了: “AlphaGo”火了！前一段时间，五场亿万人围观的人机”下棋”大战，最终机器人依托大数据与深度学习的技术优势4:1战胜了人类。胜利者告诉人们，人工智能时代真的来了。但我们必须了解到所谓大数据不单只是指单一大的数量，更重要是指数据中的完整信息。其广度、深度都要有多维性、多元化的全方位数据。单一的大数量的信息反而可以造成某些思维上的偏差，并非真正的大数据。　而這些智能化的应用，又将为人的大健康产业，包括衣食住行、生老病死都产生巨大的革命性的影响。

刚写到這里，忽然接到好友发来《自然》杂誌最新的一期封面文章:《NATURE》542, 02 February, 115-118, 并冠以”人工智能一出馬，人类医生就败下阵来”，内容正好说明问题，不妨与大家分享。 這文章里介绍了美国斯坦福的学者進行的一个实验：皮肤癌与痣长得过于相像，哪怕是资深的病理学家不到晚期都难以下定论作出诊断。现把一个分析了13万张皮肤癌图片的人工智能机器人，和21名顶尖的资深皮肤科医生一同站台打擂台。首先去分辨角质细胞癌与良性溢性角化病，结果是机器人完胜。不服气的人类要打第二次擂台，这次是提高难度，要比较恶性黑色素瘤与良性的痣，人类也同样败下阵来。全文详细有着科学数据，這说明了什么？　這是医学史上一次颠覆性的擂台！也说明了，一个好的人工智能产品开发成功，将有可能顶替无数的经历了数十年艰辛训练和培养的专才。它将是可以生产复制出不用吃喝，不用睡觉，任劳任怨，一絲不苟的智能专业机器人。可以大胆的设想: 不出多少年，每个人身边的”手机”将成为最贴心的有顶级学问的家庭医生顾问，可通晓中、西医，也会逐步帮助在家诊断疾病。而且有助于大健康的用品越来越多，越人性化。这些新颖的保护人类健康的曰用品和高端的智能的仪器都会推動社会发展，带动起一个巨大的市场。到那時，很多目前还在奋斗很抢手的第一线的专才，说不定也会碰到”下岗”的命运。這个世界发展实在太快了，真是令人既兴奋又”忧心”。

我们会看到香港人的智商IQ和大陆比不见得有特别的优势，但

社会”人性化”会高一些。香港人也更加熟悉西方文化及其处事的方式、方法。往往来自西方的人在香港比起香港人進入大陆，会更容易适应一些。在今后如将人工智能和大健康产业高度结合起来。除了智商IQ、情商EQ，中华文化中的”礼学”、”中庸”都应融入到机器人中。要”调教”出真的”好孩子”－AlphaGo。但是，如单单高智商，但却是无礼、无理、霸道的”坏孩子”的话，则会成为人类的灾难。

人工智能化的大健康产业，一定要得到香港行政首领的认可和担起着应有的主导作用。并要香港澳门地区提供良好的社会环境和人文环境以及所有配套的支持。把人工智能结合到精准医学的大健康产业，回归人性、回归情感。重塑天人合一的大自然和人类和谐共存、共生的康乐园。

這样，香港這个东方明珠不单是金融和進出口的中心，在科技上亦成为生物科技和人工智能大开发的平台，出现在世人面前再现辉煌。

因此，香港不单只是生活舒适的乐土，更是年輕人能创业、创新、园梦的地方。更多的英才将孕育在东方明珠桂冠上的”硅谷”。

香港的成功产品可以輻射到整个东南亚。也可输入到中国大陆這个全球最大的市场。而且当一带一路的西向东方列車，厚載着东西方都喜闻乐見的人性化的智能大健康的产品，可以自然地融入沿途不同的国度，包括很多第三世界的国家，终将又抵达到了西方文明之都。這也是值得很好思考的。

六、 总结

综上所述，从市场前景、竞争对手及目前一些实际情况反映出近年有关第三方检测的相关現況。由于国内发展的速度很快；人才的增長倍出；国家政令调整变化大；在生物界大健康产业的成長是来自全球的共同推動的。每半年都让人感到新的变化。投资的金额都要求越来越大，你会感到到处都会向你招手，但真正能接上地气，能落实下来真是不是容易的事情。市场始终是个关键的核心。以上的各种信息都仅仅作为抛磚引玉的参考，难免有错误和偏差，而且不同的角度，会有不同的结論。也因为各方面的变化是不可预测，都没有相同的路可走。但你会感到始终会有一股向前的推動力。努力的坚持是會有花开结果的。

郑勳華博士 2017年2月5日於广州

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Chapter 11

THE DRIVING FORCE BEHIND RETIREMENT BUSINESS: HONG KONG - CREATING A DREAM FOR YOUNG PEOPLE

退休老年創業的原動力：香港 - 為青年人製造機會達成夢想

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Overview

Returning to Hong Kong in 1973 till 2000, I devoted my time to teaching and initiating research. I endeavored to introduce the highly advanced DNA technologies to Hong Kong and regional countries, provided training to researchers in Hong Kong and the Mainland as a mean to promote research before any funding were made available then. When I retired from the HKU, I left Hong Kong but came back again to establish my own biotechnology companies from the ground up to give a platform and a place for our graduates to excel and to show that high tech industry in Hong Kong can also make money. This article summarizes my personal experience and feelings during my 60-years in Hong Kong. I hope my experience and views can serve as some guidance and encouragement for the younger generation and new entrepreneurs. This article also conveys my love and expectation of Hong Kong and the Mainland.

概要

在1973-2000年回流期間，研究資金缺乏，我只能把時間花在教學和開發研究、努力向香港、國內及鄰近地區引入先進的DNA技術，並為當地的研究人員提供培訓。當我從港大退休後，曾離開香港, 但又回來成立了我自己的生物科技公司，為我們的畢業生提供一個地方、一個工作平臺, 讓他們能夠發揮所學，同時顯示高科技行業在香港也可以賺錢，解除香港人「hi-tech瀨嘢; low-tech嘥嘢」的魔咒。這篇文章總結了我在香港60年來的個人經歷和感受。我希望我的經驗和觀點能夠為年輕一代和新企業家提供一些指導和鼓勵。這篇文章也表達了我對香港和大陸的熱愛和期待。

前言

香港是我家，也是我1973年回港工作的原因。現在香港背對日益強大的祖國、面向世界。有世界一流大學，有全球最佳的經濟體系及最高的人均儲備，無論從什麼角度去看香港也是福地，幸福生活指數應該是很高的。可惜近幾年社會面對前所未有的撕裂，因為種種原因年青人對於他們的前途只看到悲觀的一面，實在令人擔心。其實只要我們抱著正面的態度，用心經營，在困難的前面其實是一片光明的。

陳偉杰律師想我在這裡寫寫我的感受和人生歷程。我本不想答應，因為這本書是專為香港生物科技而設的論壇所以未必適宜。可是如果把個人的經歷和年青人分享，能夠為社會增加一點點正能量，為創業者分享一些經驗也好。

香港給我機會

我1938年出生於中國農村，正是日軍入侵之時。 在戰亂的日子，在農村地方即使是大富之家也未必有受教育的機會。戰勝後內亂持續，更是民不聊生。本人能在解放之年因兄長來港謀生而隨行，才有機會接受教育，所以不得不感謝新中國的成立。可是當兄長必須回鄉助父耕農，而唯一的姐姐又因作家傭而無法照顧我。我這個孤兒，只有獨自流落街頭，經過三四年的遊蕩、露宿過街頭、吃過廚餘。真的是飽受過想不盡的風霜、驚恐。最後有幸能進入佛教義學及後更被老師推薦考取「華民生」，得以免費進讀當年香港唯一的寄宿工業學校，有機會完成中學。所以老師的照顧是我一生的轉捩點，為此我也決定自己將來要當個好老師。中學畢業後，因父母來港不得不同時為照顧他們而日間工作、晚上進修，準備投考師範書院、因其不但可以進修教育訓練課程、獎學金更足夠維持一家生活。同時也投考了剛成立的中文大學。結果兩者同時成功取錄了，最後還是放棄了有薪的師範而進入中大。用學餘時間賺錢助養家中父母。

畢業後得系主任留作助教、這當然是繼續升職大學教席的好機會。但我還是希望進修。所以申請去美國升學，可是因為成績表的標準不同，沒有一間美國大學取錄。失望但不氣餒，請求教務長向加州大學代為轉達成績表標準不同的原因，結果是以暫收生取錄，必須先取得銀行存款保証才能獲美簽証入學。本著自信、有毅力、不怕辛苦，所以決定借私貸遠洋進修。結果是不到半年，証明香港學生的能力，加大從此對中大學生特別優待，在 UC Davis 爭取了不少免費交換學生學位。當然還是當時中大教務長給我的支援最管用。UCD之開先例以暫取生取錄更銘感於心。我從小學、中學、大學以至博士研究生我都得到老師的照顧，所以我對老師特別敬佩。

決定回港工作

1973年剛得到馬利蘭大學的受聘消息、老師張儀尊教授邀請我回港協助他在嶺南書院建立化學系，我義不容辭、立即放棄美國教席回來。可惜嶺南沒有把理學院延續，我才轉往香港大學醫學院任教。

回港最大的挑戰和困擾是沒有資金及適當的環境做科研究創作。在西北大學，即使是本人開發的鐮刀症(Sickle Cell Anemia)項目，憑一篇論文便能申請到兩百萬美元研究基金。在港大，即使是最有資源的醫學院當時的種子專案 (Seed Fund)只有數千元港幣。更何來資金參加國際性會議。難怪當我在面試時向系主任提出他們應該可以做些研究時，各教師都噓之以鼻。為了開展地中海貧血病的研究而遠到希臘特別參加地中海貧血的國際會議都是自資的。有了國際接觸才有機會和一流專家交流。就是到NIH進修的機會也由此而來。在此次進修中學到從DNA雜交到分子克隆的最新最完整的rDNA (重組DNA)技術訓練，把技術帶回香港。可是回港後雖然得到些支援，研究資金也不外乎數萬元，在80年初已是很大的鼓舞，不過這些資金就只能夠買到少量的限制性內切酶，不可能真正進行較大規模的實驗。幸好有NIH慷慨捐贈才能繼續進行一些工作。有見及此，本人深信必須從根本的啟蒙著手。於是決定從開展訓練人才方面著手，把技術發放給區內的其他科學工作者參與。最先是協助上海兒童醫院建立DNA實驗室，繼而復旦、協和及北京、上海中科院等 (圖一) 都表示歡迎。最好的辦法還是聘請國際一流專家來港作訓練班，培訓更多年青的科學家開始研究工作，增加社會大眾的關注和認識。與此同時，世衛文教處(UNESCO)剛剛開始了rDNA的訓練課程，由哈佛大學的始創人任教。為此本人和兩位同事Dr. VMS Lam 和Dr. Lydia Cheng到處參加國際會議，與世衛文教處負責人接觸、同時得到幾位哈佛大學教授、冷泉港和羅氏藥廠分子研究所專家首肯，親自來港授課 (圖二) 。 因要籌備大量儀器、試劑及各項行政所需費用、特別是中國十多位年輕科學家旅宿費等、所需資金比預期大。為此足足花了兩年時間，成功完成訓練了第一隊來自中港臺及遠東星馬泰韓等各地的rDNA研究人員(圖三)。可幸的是這些人現在都已成為傑出的科學領頭人。其後香港大學的分子研究所也是由此以生。再得到復旦大學遺傳學泰斗談家楨的垂青、引薦與香港大學結成姊妹大學關係。

我回港的目的不是要成為出色的科學家，目標是把國外尖端科技引進香港和祖國，同時幫助訓練更多的人才。因為本港及本人的實際條件與國外一級水準有差距，所以更多著眼協助國內大學研究。同時為國內專才介紹國外進修的去處。在可行範圍內向國內提供資源特別是一些難得的研究材料如同位素、限制性內切酶等使他們能夠展開研究工作。本人的實驗室提供短期訓練等等。同時也接受國內有質素的研究生來港受訓。地方涵蓋全國從北京、天津、上海、河南、長沙、廣州、西安、成都、重慶遠至蒙古、寧夏。只要我能幫的我都願意。我想2000年前這樣的做法對國內一些單位或能有所幫助，這是我的目標。也是我對香港和中國唯一可以做的微薄貢獻。

港大退休後的生活

在2001年退休回美國看兒女時有基金經理人提出請以本人的專利創業。說實話、加州灣區是高科技公司的夢幻之城，是基金和人才的搖籃地，應該是創業最理想的地方，沒有理由不去接受。可是這更啟發了在香港創業的念頭。我雖非生於斯但長於斯、香港是我家，如果有機會創業，應該在香港創業。所以我拒絕了在有利條件的加州灣區創業。雖然香港人當時全無創業基金我也願意在港發展。其實最重要的還是：作為香港人，回顧來港幾十年、眼看著香港由一個漁港、漸漸變變國際大都會。眼看著香港有最好的社會環境、有最好最有創意的人群（據說香港人IQ全球最高）、有世界一流學府、金融中心和最完善制度。科技方面，香港就有諾貝爾得獎者、提名人。有中國、美國、英國科學院院士。有多位女科學家得國際獎者，中國最近的兩個未來科學大⿴的生命科學大⿴就落在香港中文大學的盧煜明教授手上。所以理論上矽谷等科技中心應該可以在香港有立足之地。香港實在人傑地靈，六七十年代成為世界第一的有李嘉誠的膠花、紡織以至於電子手錶等。可是80年後香港的工業卻是每況愈下。時至今日香港工業只有GDP的1%。試問我們的畢業生可以去哪裡?以以色列為例，人口相若、GDP 相近、雖然要用大量軍費開支，但是其科技發展一日千里，是世界的表表者。同樣，新加坡是華人社會，沒有中國大陸的支援，科技發展還是遠遠走在前面。再看近鄰深圳，三十年前是個廢墟，但最近的預測兩年後它的GDP將會追過香港。如果上海能夠在四五年內追成東方的矽谷。香港為什麼不能有點作為?我實在不甘心。

有見及此，本人不自量力，以退休之年留港創業。以香港大學合夥人身份建立MGC分子診斷中心。其後成立了凱普生物科技(HybriBio)，希望為我們的畢業生建造一個工作的地點、平台，使他們有發展空間。在SARS的低迷時候、我們也為香港製造職業。只因凱普決定遷入中國，本人才決定建立⿴雅高科技公司繼續為香港畢業生提供就業機會。

經過10年的艱苦努力，達雅高已建立成四間公司、以香港為總部、員工超過百人。同時在廣州生物島的百皋醫療檢驗所是現今唯一的外資全資持有的協力廠商醫療檢驗所，為祖國人民提供優質檢驗服務。我們更建立了馳安GMP 廠房、向祖國及國際提供高本質產品及服務。最重要的是我們的公司為員工訓練了不少企業人才培養創業精神。雖然昔日員工今天變成競爭對手，但他們也有開創新的科技產品及服務。有更多人把香港科技開發起來，這是我最希望看到的。 正是我80年用訓練班把rDNA技術引進遠東發展及傳播的目的。

回顧10年，真是困難重重、有血有淚。香港雖然非常富有、人傑地靈。但是說到高科技產業投資他們便耍手擰頭，因為大家都相信:「hi-tech瀨嘢;low-tech嘢嘢」。所以我知道在港創業的商業模式必須從開始便要有收入來支援業務。凱普的成立如此。達雅高也必須如此。所以我和拍檔王舜仁先生合資百萬港元，只夠購買一些必須的舊儀器提供即時檢驗服務、以產前檢查唐氏的染色體篩查為收入基礎，支援發展為快速的DNA檢驗三倍體與傳統染色體相互核實，並得到醫生病人的信任。同時把本人的導流雜交⿴利技術研發產品銷售世界。其後幸好得到美國加州灣區朋友的支援，給予少許起動資金。使我們的六位員工得繼續研發產品。正正是在最困難的時候、員工更一心一意投入工作，以最快速度研發分子檢驗服務產品、務求盡快得到收益。當中經歷多次經營危機、公司資金短缺、金融經濟危機等、我們的員工也不離不棄，更是迎難而上度過危機。達雅高有今日，完全是我們的員工不分你我全方位合作共同拼搏而得來的。其次是各位股東合夥人。老實說過去十年的收入盈利96%都用作公司產品研發和擴展。他們的犧牲和支援是公司的最大資源。

現在我們可以很自豪地說已經為我們的香港畢業生建立了一個工作地方平台，也達到了本人留港創業的第一個目標。並且引證了生物工程科技在香港都能賺錢的先例。我們的下一個目標是貫徹公司的基本企業文化和基本價值觀，提升公司的品牌形象，確立（IQ；WWW）「高誠信，高質素」 和「服務社會」的宗旨。 所以以後的10年我們的任務更艱巨。在此我誠心多謝他們過去的貢獻。同時希望他們為公司、合作夥伴和顧客社會創造福利的「三贏」局面。公司的未來以及香港的未來都在年青人手中。

我希望大家知道我們公司檢驗服務項目、試劑產品多是由本公司自我研發出來的，有自己的專利的技術和產品。現在已有試劑盒20多種銷售。在沒有足夠資金的支援下，研發的速度、精確度等可能都未算最理想。但是已達銷售世界各地水準。 剛過去的十週年紀念日就有20多國家分銷商參與我們的盛宴。
希望在未來的 10 年我們年青能為公司研發出更好、更新的產品成為香港國際認可的品牌。本人更希望有更多的公司成功進軍國際，使香港成為國際級的另一個生物科技創業園區，給我們的年輕人一個用武之地。 成就更多青年企業家。 這才是我的夢想。

我想向年青人說兩句

香港現在有足夠的人才、有足夠資金及融資管道。硬體如科學園、科創局和港科院已成立。還有河套地區的科技園即將建立起來。在政策上，無論是政府、大學、工商界現已體會到科技之重要性。以政府的巨額盈餘下將會向創新科技大量注資。 你們在科技領域的前途比起十年和二十年前的環境已提升不只百倍。

不過成功與否卻是全在你們自己手上。以我過往經歷，我曾多次說過高科技在香港創業是艱苦而孤獨的。雖然現在已有所改善，但你們必須有心理準備，成功創業者背後必須具備有以下幾個條件：

1. 要有「破釜沉舟」的決心。我看過很多孵化公司的成功與失敗。無論是在國外、特別是在香港，最大失敗原因是因為創辦人太容易得到基金，沒有好好計劃開發持續收入來源，一但因為技術問題未能如期達標，結果因資金用盡而失敗。其次是認為創業可以是兼職的。有資金可以聘用員工代勞、自己可以指指點點、不必用心，成功可以繼續，失敗了也不要緊，反正不是自己的錢。當然很多是因不能抗拒的原因而失敗的。無論如何，希望大家在創業前先好好思量。其實作為員工的也一樣，不能專注用心的最後可能一事無成。

2. 要有「不怕失敗」的心態和「堅毅不屈」的精神。我認識不少聰明能幹、見多識廣，滿腹計劃，但每每因怕萬一失敗而退縮。其實以本人的公司為例，百份之九十的嘗試是失敗收場的。當然大部分是因為資源缺乏而作罷，但是人為的因素實在不能忽略。研發的困難每每比在學校的基礎⿴究更具挑戰性。商場變化大，我們必須和時間競賽、與競爭者競賽、分秒必爭。所以必須要有堅強的鬥志。正如香港 拳王「神奇小子」曹星如一樣，不能氣餒。

3. 不能過於貪婪。成功的另一因素是要有「海量胸懷」，凡事向大處、遠處看，要高瞻遠矚。在公司內外增加合作空間、先把事情做好做大，哪怕利益不回來。 把餅做大了大家收益便會更大。

4. 最後還是 「用心 」最重要 。 這是上至企業家下至員工成功的必要條件。

我誠心希望你們好好想想「香港的特有地位、堅守基本核心價值觀」。只要我們「用心」去做，必定成功。我相信來屆政府，科技處、高校、工商企業家都會支援你們。使香港能成為科技中心。我誠心希望各方共同發展，把怨氣變成力量，把正能量提升，共同努力發揮香港人的潛力。香港的未來就在你們年輕人手中，只有同心協力、香港才會更好。

居港六十年的經歷與感受

我十歲來香港的時候人口不到五十萬。睡過幾年街頭、吃過別人吃剩的飯菜，飽受貧困的煎熬。所以在中小學時已經積極參與世衛的分衣派米活動。中學畢業後至大學進讀期間和父母一家三口住的房間不到八十呎、只有六呎高樓、頭上是另有人家。比現在的劏房更差。當時各區山邊木屋林立、常有火災。為了解決住屋問題政府開始建立只有公共衛生間、樓高的七層公屋。當時香港人不但為自己的

生活而努力工作，還要早晚無時不息的想法救助在國內的親友，我也不時擔負比自己還重的東西回鄉供養他們。在我的印象中貧窮的社會反而和諧相處。
只因為留學國外正好避過了文革之亂。可是自從基辛格破冰之旅，我有幸帶著兩歲多的兒子在芝加哥歡迎沈陽雜技馬戲團到美表演及乒乓外交、對祖國的開始興盛而感到驕傲。70年代回港定居，正是香港向國際城市極速發展的時候，無論是金融、建築、旅遊，特別是工商業的發展也是東方之首。當時如能把國外引入的工業使其核心技術留下建立起來，今天的香港可能和以色列、新加坡、台灣和南韓等不遑多讓。可惜政府的短視造成了地⿰獨大局面。這當然可以歸咎殖民統治而不能自主。

說實話，回歸以後，董特首的政策現在看來還是最有遠見的。我最樂見的是他的科技建設。其八萬五的房屋計劃雖然比較進取，可是如能落實一半，現在已建成五十萬個房屋單位，即使每戶是2至4人，也能已使大部分居民都有容身之所了。何懼國內人來把地價推⿰。可惜因天災人禍、大部分的計劃都未能實行。外來的天災如金融風暴和SARS我們無法控制，但是我們還是很快戰勝它們了。最大的問題在於人和。在樓市最低沉的時候，大家會把注意力轉移到科技創新去發展，這正是董特首成立創新科技處的目的。孫九招似乎把樓市救了，但這不但把科技轉型的一線希望完全毀滅了。最壞的是十多年停建房產使樓價飆升，加上近年內地人大量資金流入，使港人特別是年輕人無法上車，是導至現今社會撕裂的主要原因。當然，政治的不和諧，使撕裂更甚。

很多人對政治冷感甚至厭惡，這是普通人性。本人也從不過問政治，只有每四年參與選舉投票就算。如今看來不問政治是錯誤的。其實政治乃眾人之事，不得不去關心，否則可能讓一些少數人把社會推向極化。在SARS期間我曾在信報月刊寫過對董特首的敬佩，但提及他從未有和民主派接觸、對其政治手段確實有點兒失望。去屆梁特首的強硬政策，使社會撕裂更甚。誠然，孤掌難鳴。不能只看一面。民主黨人特別是梁某等在上海中國國土、在宣誓台上的行為，民主黨派不但不應支持，更應曉以大義。我相信若能互相尊重，831和最近的釋法多不會發生。佔中之初本也得到相當市民支持、同情。對表達意見有積極作用。但是長期便成擾民、濫用暴力更是於法理不合，絕對不能容忍。發起人沒有全力勸止，非常失望。

政治是要把不同政黨的意見經過互辯而作出妥協，使社會達成共識使有利人民的政策付諸執行，以利民生。雙方政見不同，也必須溝通才能有機會得到共識。至少是和而不同，才能和諧共處。才可讓市民向前邁進作福民生。年輕人看得到希望，哪有作反之理。希望本屆特首能為我們從新開路，為香港人建立幸福家園。也能夠以特區的成功証明我們的開明理性是最有效引証鄧小平的遠見正確而超然。以「一國两制」為中華民族大團結開路。

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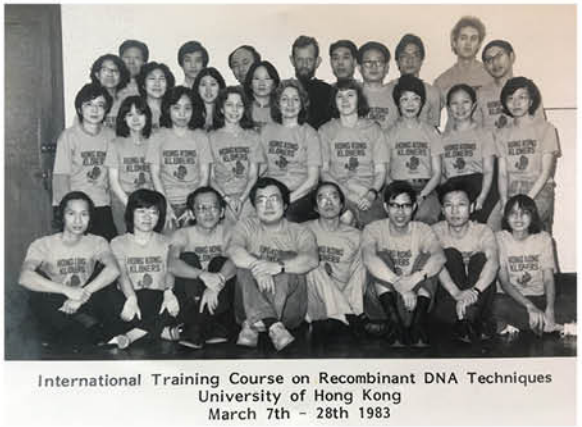
▲ 拜會上海中科曹天欽和李載平院士

▲ Genentech 始創人是生物工程先行者



▲ 1983年在遠東舉辦首次由世衛文教處支持的rDNA訓練班得到哈佛、冷泉港及羅氏藥廠專家親自來港大傳授技術

▲ 湘雅謝慎思教授來港大為我們找出地中海貧血珠蛋白起動因子蛻變的首例。
展開DNA研究、教育是我們的任務和使命

▲ DiagCor在2006起步、雖幾經艱辛我們終於為香港年青人創造立足之地，除了達雅高我們的員工更散播香港科技創業

▲ 達雅高把高科技必輸的咒語打破。 如今香港更有足够的條件，
但願香港能順利發展年青人更多希望社會和諧幸福

Chapter 12

THE REFORM OF CROP-VARIETY REGULATIONS IN CHINA AND ITS IMPLICATIONS FOR PRIVATE INVESTMENT

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ABSTRACT

The Chinese State Council issued an opinion in 2011 concerning the reform of its crop variety regulation, and the revision of relevant laws and regulations follow suit. Unlike other developing countries, foreign participation in the development of main crop varieties has been scant in China. This paper examines measures taken by the Chinese government on the reform of seed regulations in recent years, with its focus on the trend for the issuance and revocation of certification for planting nationwide. Our study found that the number of certification granted for nationwide popularization showed a trend of reduction. A large proportion of certificates for nationwide popularization issued in the early 2000s have been revoked in recent years. They were issued in a period where the seed sector in China were dominated by public institutions and the standard for granting the certificates were ill defined or poorly understood. The recent reform was expected to reduce farmer confusion by excluding a large number of main crop varieties which were previously granted from the seed market. The government's determination on enforcing valid plant variety rights would increase the confidence and reduce the uncertainty for private investment. The government also encouraged merger, acquisition, and privatization in the seed sector to increase competitiveness. These measures were potentially beneficial for private investment in the seed industry, including investment from Hong Kong.

Keywords: main crop, China, seed, consolidation, vertical integration.

1. Introduction

China is very rich in germplasm resources of crops. It ranks third in the world in terms of germplasm resources, only second to Brazil and Colombia.[4] It was estimated that China has more than 50,000 local rice varieties and 20,000 soybean varieties.[4] Seed is considered national resources in China and it is the government's obligation to protect the resources.[i]

The Chinese government deemed the seed industry as its national strategic and fundamental industry.[21] Although China, India and Brazil are among the developing countries that have large agricultural research systems with significant plant breeding capabilities,[20] insufficient innovations, weak competitiveness among domestic seed companies, and loopholes in seed management have hampered the development of the seed industry in China.[24]

Under the Chinese Seed Law, three parallel systems are concurrently in charge of different aspects of regulations on crop varieties, namely the examination and issuance of new crop varieties, the review and approval of main crop varieties for nationwide popularization, and the regulation of agricultural genetically modified plants. The parallel systems in China were apparently designed for rigorous regulation and preservation of seed resources. Nonetheless, chaos and confusion in the market ensued concerning the denomination of crop varieties because of the lack of communication among the parallel systems.[15] As a consequence, the same crop variety may have various name designations in different systems.

Seeking to redress the situation, the Chinese State Council issued an opinion in April 2011 concerning the enhancement of its modern crop seed industry.[21] The opinion was considered the inception of China's recent reform on its crop variety regulation. In addition to the improvement of competitiveness by encouraging vertical and horizontal integration of domestic seed companies, the Chinese government also seeks to strengthen crop variety innovation and close the legal loopholes in seed management. On the other hand, although multinational companies' technologies were far ahead of Chinese seed companies, they did not enjoy more advantages in terms of marketing in China because of constrained seed markets, ineffectual intellectual property rights, and various government regulations.[9,6]

This paper examines measures taken by the Chinese government on the reform of its seed regulations in recent years. Principal measures taken under the reform can be categorized as either preventive mechanism or exit mechanism. To be better informed about the actual effect of China's reform on seed regulations in recent years, we employed empirical studies to reveal the trend for the issuance and revocation of certification for nationwide popularization. In particular, the relevant agency in China, by following the State Council's explicit instruction in 2011, for years have raised the standard for the issuance of certificates for nationwide popularization resulting in steady decline of the number of issuance in recent years.

i Art. 8, zhonghua renmin gongheguo zhongzi fa 2013 (Seed Law of the People's Republic of China 203).

2. Background

China is the second largest seed market in the world after the United States.[1] The Chinese government identified the seed industry as the national strategic and fundamental industry.[21] However, insufficient innovations, weak competitiveness among domestic seed companies, and loopholes in seed management have hampered the development of the seed industry in China.[24]

Although the size of the commercial seed market in a country has an important bearing on the incentives for private investment in the development of locally-bred crop varieties,[20] only 1% of research and development budgets of multinational companies were spent on crops valuable for the developing world.[18] Developing countries need to develop crop varieties best adapted to their local environment to sustain food security. In particular, China, India and Brazil are among the developing countries that have large agricultural research systems with significant plant breeding capabilities.[20]

However, the Chinese market was congested with seed companies with little or no research capabilities. Many developing countries have policies precluding private sector and foreign participation in plant breeding.[8] For instance, agricultural research in China has been dominated by public agencies staffed and financed largely by the government, though the demarcation between the public and private sectors is sometimes difficult to discern.[9] In 2011, while China had more than 8,700 seed companies, only about 100 companies possessed the capacity to undertake research.[6] By contrast, there were only around 100 seed companies in the United States, but they accounted for more than half of the total profit of the global seed industry.[6]

The enhancement of the productive powers of improved crop varieties is the physical embodiment of plant science and molecular biology.[2,18] In addition to insufficient innovation, weak competitiveness among domestic seed companies and loopholes in seed management were also identified as the major problems hampering the development of Chinese seed industry.[24] China has a long history of policy promoting vertical integration in the agricultural sector, by integrating production with processing and marketing, to raise farmers' income and to promote commoditized agriculture to meet growing urban demands as early as in the 1990s.[23] The Chinese government also believes that the increase in market concentration by encouraging horizontal integration among firms would foster the domestic seed companies' competitiveness against multinational companies.[21] In recent years, since the Chinese State Council's announcement of its determination to enhance the development of the seed industry

in 2011,[21] the number of seed companies had reduced to 6,296 due to the government's encouragement of merger and acquisition,[24] and the vertical integration of breeding, producing and marketing (State Council, 2011).[21]

Measures adopted to encourage merger and acquisition include raising the amount of registered capital required for operating seed companies.[21] For instance, Bt-cotton varieties have been marketed in China since 1997, and they were grown on about 70 per cent of the total Chinese cotton-growing area.[5,17] Since October 2011, companies engaged in transgenic cotton seed production and operation are required to have registered capital in excess of RMB 30 million.[14] While there were more than 6,000 seed companies in China, only around 300 seed companies had registered capital greater than RMB 30 million, which was approximately equivalent to $4.9 million USD.[ii]

The Chinese government also adopted other measures to strengthen crop variety innovation and close the loopholes in seed management. Measures to promote innovation include the stricture of the approval for nationwide popularization of main crop varieties. The focus of these measures to close regulatory loopholes is primarily on the improvement of communication among parallel regulatory systems and the adoption of a uniform system for variety name designations.

ii Staff reporter, 2014. Monsanto, Sinochem JV to become China's seed industry giant. Want China Times, 9 February 2014. <http://www.wantchinatimes.com/news-subclass-cnt.aspx-?id=204029000057&cid=206> (accessed on 1 October 2014).
iii Art. 2, zhonghua renmin gongheguo zhongzi fa 2013 (Seed Law of the People's Republic of China 2013).
iv Art. 5, zhonghua renmin gongheguo zhongzi fa 2013 (Seed Law of the People's Republic of China 2013).
v Art. 14, zhonghua renmin gongheguo zhongzi fa 2013 (Seed Law of the People's Republic of China 2013).
vi Art. 10, zhonghua renmin gongheguo zhongzi fa 2013 (Seed Law of the People's Republic of China 2013).
vii Art. 8, zhonghua renmin gongheguo zhongzi fa 2013 (Seed Law of the People's Republic of China 2013).
viii Art. 2, zhonghua renmin gongheguo zhongzi fa 2013 (Seed Law of the People's Republic of China 2013).
ix Id.
x Id.
xi Art. 27, zhonghua renmin gongheguo zhongzi fa 2013 (Seed Law of the People's Republic of China 2013).

3. The parallel systems

The Seed Law is the highest legal guidance concerning the government's regulation of the seed industry in China. As provided in Article 2, the Seed Law applies to all activities involving the "breeding, selection, production, business operation, usage, and management of seed" in the country. Under the Seed Law, three parallel systems in China are concurrently in charge of different aspects of regulations on crop varieties.

China's central government is authorized under the Seed Law to formulate a system for the examination and issuance of Plant Variety Protection (PVP) certificates,[iii] a system for the review and approval of main crop varieties before they can be popularized,[iv] and a system for the regulation of agricultural genetically modified plants,[v] respectively. Nonetheless, confusion in the market ensued regarding the identity of crop varieties because of the absence of a uniform system for variety name designation across the parallel systems and the lack of communication among the agencies. This paper has its focus on the approval for nationwide popularization for crop varieties.

The Chinese government has sovereignty over the seed resources within its borders.[vi] Seed is deemed a national resource in China, and the government has an obligation to protect the resources.[vii] Under the Seed Law, seed is defined broadly as any "materials of crops and forest trees used for planting or propagation."[viii] Therefore, not only seed grains, but fruits, roots, stems, seedlings, buds and leaves may also be considered "seed" under the law.[ix] The Seed Law governs any activity in China involving the breeding, selection, production, business operation, usage, and management of seed.[x] The law authorizes the Chinese government to promulgate rules such as the Regulations on the Protection of New Varieties of Plants, the Rules for the Certification of Main Crop Varieties, and the Regulations on Administration of Agricultural Genetically Modified Organisms Safety, to fulfill the stated mission of protecting the nation's seed resources.

Regardless of the broad spectrum of various regulations and certification requirements promulgated under the Seed Law, the Law exempts farmers from selling or exchanging residual seeds they have previously bred and used on the market without the need of any operating license.[xi] Similarly, the Regulations on the Protection of New Varieties of Plants, which are the rules governing the examination and issuance of PVP certificates, also have provisions providing farmers with the privilege of using seeds they previously bred for propagating purposes without violating the rights of the variety holder.[xii]

Moreover, the Regulations further exempt activities involving the exploitation of

protected varieties for breeding, as well as other research activities, from being found as infringement.[xiii] Otherwise, the holder of variety rights can exclude any entity or individual from producing or selling the propagating material of the protected variety for commercial purpose, or using the protected variety's propagating material repeatedly to produce the propagating material of another variety for commercial purposes.[xiv]

Plant and animal varieties are regarded as unpatentable and the only avenue for breeders in China to protect new plant varieties is by seeking PVP certificates.[3] The breeders of new plant varieties may apply for PVP certificates if the varieties meet certain criteria. The government agency in charge of the examination and issuance of plant variety rights in China is the Office for the Protection of New Varieties of Plants. Similar to the plant variety protection laws in other countries, the breeder of a new plant variety would receive a certificate only if the plant variety is new, distinct, uniform, stable, and has an adequate name designation,[xv] provided that the new variety is part of botanical genera and species included in the national list of protected plant varieties.[xvi] From June 1999 to April 2013, the Chinese government had published 9 lists, and overall 93 plant species are eligible for protection. Among the listed categories of plant, rice and corn were included since 1999; wheat and soybean were added in 2000, while cotton was not listed until 2005.

Nonetheless, the issuance of a PVP certificate does not grant the holder of the new variety any right to mass produce, sell, or popularize the protected variety in China. These activities are subject to review and approval under other national laws and regulations,[xvii] even if the Regulations on the Protection of New Varieties of Plants have provided the holders of PVP certificates with the right to exclude others from producing or selling the protected varieties.[xviii] In other words, though the holder of a PVP certificate can legitimately exclude others from selling or producing the protected variety, the right holder is not permitted to sell, mass produce, or disseminate the new variety without seeking further approval from another government agency.

The Rules for the Certification of Main Crop Varieties established the system for the review and approval of main crop varieties before the particular varieties can be popularized. Under the Chinese Seed Law, main crops are referring to rice, wheat, corn, cotton, and soybean.[xix] As effective in February 2014, the amended Rules prescribe two additional main crops, namely oilseed rape and potato.[xx] In this paper, main crops are referring to the five categories of crops prescribed prior to 2014 under the Seed Law.

The National Crop Variety Certification Committee, as established by the Ministry of Agriculture, is in charge of the review and approval of main crop varieties for nationwide popularization.[xxi] The ownership of PVP certificate is not a prerequisite for an applicant to seek the review and approval of a main crop variety for nationwide popularization. However, similar to the examination for the issuance of PVP certificates, the review and approval of main crop varieties for nationwide popularization also require that the varieties meet criteria similar to the criteria for the issuance of PVP certificates, such as the variety being distinct, stable, uniform, and adequately denominated, provided that a multipoint cultivar comparative trial in the same ecological region for more than two years has been conducted.[xxii] To be qualified for nationwide popularization, the variety needs to be tested on its high multiplication rate,[xxiii] stability in high yield, adaptability, and stress resistance in field.[xxiv]

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xii Rule 10, zhonghua renmin gongheguo zhiwu xinpinzhong baohu tiaoli 2013 (Regulations on the Protection of New Varieties of Plants of the People's Republic of China 2013).

xiii Id.

xiv Rule 6, zhonghua renmin gongheguo zhiwu xinpinzhong baohu tiaoli 2013 (Regulations on the Protection of New Varieties of Plants of the People's Republic of China 2013).

xv Rule 14-18, zhonghua renmin gongheguo zhiwu xinpinzhong baohu tiaoli 2013 (Regulations on the Protection of New Varieties of Plants of the People's Republic of China 2013).

xvi Rule 13, zhonghua renmin gongheguo zhiwu xinpinzhong baohu tiaoli 2013 (Regulations on the Protection of New Varieties of Plants of the People's Republic of China 2013).

xvii Rule 5, zhonghua renmin gongheguo zhiwu xinpinzhong baohu tiaoli 2013 (Regulations on the Protection of New Varieties of Plants of the People's Republic of China 2013).

xviii Rule 6, zhonghua renmin gongheguo zhiwu xinpinzhong baohu tiaoli 2013 (Regulations on the Protection of New Varieties of Plants of the People's Republic of China 2013).

xix Art. 74(3), zhonghua renmin gongheguo zhongzi fa 2013 (Seed Law of the People's Republic of China 2013).

xx Rule 3, zhonghua renmin gongheguo zhuyao nongzuowu pinzhong shending banfa 2014 (Rules for the Certification of Main Crop Varieties of the People's Republic of China 2014).

xxi Rule 4, zhonghua renmin gongheguo zhuyao nongzuowu pinzhong shending banfa 2014 (Rules for the Certification of Main Crop Varieties of the People's Republic of China 2014).

xxii Rule 11(2)-(6), zhonghua renmin gongheguo zhuyao nongzuowu pinzhong shending banfa 2014 (Rules for the Certification of Main Crop Varieties of the People's Republic of China 2014).

xxiii The ratio of quantity harvested to the quantity sown.

Among the five main crop varieties, cotton is different than the other four main crops in that genetically modified cotton varieties were introduced in China as early as in the 1990s and were widely grown since then. Bt-cotton varieties have been marketed in China since 1997 and they were grown on about 70 per cent of the total Chinese cotton-growing area.[5,17] The Rules for the Certification of Main Crop Varieties specifically require that, for applications seeking approval for nationwide popularization of transgenic cotton varieties, the applicants should provide the review committee with the safety certificates of agricultural genetically modified organisms.[xxv]

Agricultural genetically modified organisms, including transgenic crops and seeds, are subject to the government's supervision under the Regulations on Administration of Agricultural Genetically Modified Organisms Safety.[xxvi] Activities involving the selection, breeding, testing, examination and popularization of transgenic plant species are strictly regulated in accord with the State Council's instruction.[xxvii] Without obtaining licenses from the government, the production, processing, and marketing of genetically modified plant seeds are prohibited.[xxviii] Obtaining the safety certificate of agricultural genetically modified organisms is also a prerequisite prior to any examination, registration, evaluation or approval conducted as provided in other laws and regulations.[xxix] With very few exceptions, most certified genetically modified crop varieties were transgenic cotton varieties.[17, xxx]

The parallel systems in China were apparently designed for rigorous regulation and preservation of seed resources. Nonetheless, chaos and confusion in the market ensued concerning the denomination of crop varieties because of the lack of communication among these systems.[15] As a result, the same crop variety may have various name designations in different systems.[15] Moreover, it is worth noting that both the Regulations on the Protection of New Varieties of Plants and the Rules for the Certification of Main Crop Varieties have prescribed the distinctiveness, the stability, and the uniformity of crop varieties as part of the criteria for the issuance of PVP certificates and nationwide popularization certificates, respectively. The inconsistency regarding the assessment of same crop varieties by two government agencies due to the lack of communication between parallel systems may further exacerbate the confusion and chaos in the market. Seeking to redress the situation, China's State Council issued an opinion in April 2011 concerning the enhancement of its modern crop seed industry.[21] The opinion was considered the inception of China's recent reform of its crop variety regulations.

4. The reform

The Chinese State Council issued a broad-spectrum opinion in April 2011. Measures being undertaken in the opinion include, among others, adopting a uniform system for variety name designation, improving and raising the standard for the issuance of nationwide popularization certificates for main crop varieties, and adopting an exit mechanism for main crop varieties previously approved for nationwide popularization which are no longer suitable for mass planting in the country.[21]

The adoption of a uniform system for variety name designation is a preventive measure sought to maintain the seed market in good order. As effective in April 2012, the applicants are required to file an affidavit affirming that the name designation for the crop variety at issue is the same for the application of PVP certificate, the application for nationwide popularization certificate, and the application for safety certificate of agricultural genetically modified organisms.[xxxi] If the system is adequately implemented, the problems of "same name designation for multiple varieties" or "multiple names for same variety" currently in the seed market would eventually be resolved.

The State Council instructed a preventive measure by raising the standard for the examination of main crop varieties to preclude "trivial modifications" of existing varieties from being granted certificates for nationwide popularization.[21] The State Council also instructed to enhance the enforcement of protections on plant variety rights.[21]

xxiv Rule 17, 19, zhonghua renmin gongheguo zhuyao nongzuowu pinzhong shending banfa 2014 (Rules for the Certification of Main Crop Varieties of the People's Republic of China 2014).

xxv Rule 12 (6), zhonghua renmin gongheguo zhuyao nongzuowu pinzhong shending banfa 2014 (Rules for the Certification of Main Crop Varieties of the People's Republic of China 2014).

xxvi Rule 4, zhonghua renmin gongheguo nongye zhuanjiyin shengwu anquan guanli tiaoli 2011 (Regulations on Administration of Agricultural Genetically Modified Organisms Safety of the People's Republic of China 2011).

xxvii Art. 14, zhonghua renmin gongheguo zhongzi fa 203 (Seed Law of the People's Republic of China 2013).

xxviii Rule 19 and 26, zhonghua renmin gongheguo zhuyao nongzuowu pinzhong shending banfa 2014 (Rules for the Certification of Main Crop Varieties of the People's Republic of China 2014).

xxix Rule 17, zhonghua renmin gongheguo zhuyao nongzuowu pinzhong shending banfa 2014 (Rules for the Certification of Main Crop Varieties of the People's Republic of China 2014).

xxx See zhongguo shengwu anquanwang (Website of Biosafety in China). <http://www.stee.agri.gov.cn/biosafety/spxx/> (accessed on 3 October 2014).

The State Council advised an exit mechanism for the revocation of certificates previously granted for the nationwide popularization of main crop varieties which were found not suitable for mass planting in the field due to lax in the process of examination or because of environmental change.[21] The newly revised Rules for the Certification of Main Crop Varieties, as effective in February 2014, provide an exit requirement for main crop varieties previously certified for nationwide popularization if insurmountable defects were found during the use of the variety; the identifying properties of the variety have seriously regressed; or the holder of the certificate did not submit standard sample as the review agency has requested.[xxxii] The adoption of an exit mechanism is a measure to redress the confusion concerning the identity of crop varieties which closely resemble one another on the seed market. The confusion may also arise from the situation where the same crop variety is being certified under multiple name designations, either by the same or different government agencies.

In sum, principal measures taken under the reform can be categorized as either preventive mechanism or exit mechanism. To be better informed about the actual effect of China's reform on seed regulations in recent years, we employed empirical studies to reveal the trend for the issuance and revocation of certification for nationwide popularization.

5. Data sources and key findings

In this study, the data and information concerning the number of main crop varieties approved for nationwide popularization are compiled from various public notice issued by the Chinese Ministry of Agriculture. Similarly, the data and information concerning the number of main crop varieties previously approved for nationwide popularization but later revoked are also compiled from various public notice issued by the Ministry of Agriculture.

Our study found that the number of certification granted for nationwide popularization showed a trend of reduction in recent years. From 2008 to 2013, the Ministry of Agriculture published eight lists of revoked nationwide popularization certificates previously approved for main crop varieties. A notable trend, as evident in **Figure 1a**, shows that the aggregate number of certification granted for the five main crops per year steadily reduced since 2009, although the number of certification issued by category of plant fluctuated (**see Table 1**).

Table 1. Number of major crop varieties approved for nationwide popularization per year from 2001 to 2012

Year of grant	Corn	Rice	Soybean	Wheat	Cotton	aggregate
2001	13	36	12	13	5	79
2002	1	0	0	0	5	6
2003	79	88	32	45	2	246
2004	46	61	7	25	3	142
2005	51	59	26	22	20	178
2006	68	75	29	32	18	222
2007	36	52	25	30	18	161
2008	29	45	30	20	25	149
2009	14	52	30	33	23	152
2010	24	55	19	22	9	129
2011	25	29	19	21	15	109
2012	20	44	7	16	6	93

Source: the data were compiled from various public notice issued by the Chinese Ministry of Agriculture (MOA), namely gonggao di 171 hao (29 Aug. 2001), di 191 hao (2 Apr. 2002) di 248 hao (8 Jan. 2003), di 308 hao (6 Nov. 2003), di 413 hao (19 Oct. 2004), di 498 hao (30 Apr. 2005), di 516 hao (24 Jun. 2005), di 844 hao (9 Apr. 2007), di 928 hao (14 Nov. 2007), di 943 hao (7 Dec. 2007), di 1072 hao (7 Aug. 2008), di 1243 hao (28 Jul. 2009), di 1453 hao (9 Sep. 2010), di 1655 hao (8 Oct. 2011), di 1674 hao (18 Nov. 2011), guo pin shen ban [2012] 27 hao (27 Nov. 2012); 2005 nian guoshen xiaomai pinzhong (Wheat Varieties Approved for Nationwide Popularization 2005), http://www.chinaseed114.com/seed/1/seed_110.html [accessed on 8 Oct. 2014]; 2006 nian guoshen xiaomai pinzhong (Wheat Varieties Approved for Nationwide Popularization 2006), http://www.chinaseed114.com/seed/1/seed_116.html [accessed on 8 Oct. 2014]; 2008 nian guoshen xiaomai pinzhong jianjie (Wheat

xxxi Rule 6, zhonghua renmin gongheguo nongye zhiwu pinzhong mingming guiding 2012 (Rules for the Name Designation of Agricultural Plant Varieties of the People's Republic of China 2012).

xxxii Rule 36, zhonghua renmin gongheguo zhuyao nongzuowu pinzhong shending banfa 2014 (Rules for the Certification of Main Crop Varieties of the People's Republic of China 2014).

Varieties Approved for Nationwide Popularization in 2008 and the Introduction), http://www.chinaseed114.com/seed/10/seed_47848.html [accessed on 8 Oct. 2014]; 2009 nian guojia shending xiaomai pinzhong jianjie (Wheat Varieties Approved for Nationwide Popularization in 2009 and the Introduction), http://www.chinaseed114.com/seed/6/seed_25418.html [accessed on 8 Oct. 2014]; 2010 nian guoshen xiaomai pinzhong mulu ji jianjie (List of Wheat Varieties Approved for Nationwide Popularization in 2010 and the Introduction), http://www.chinaseed114.com/seed/10/seed_47871.html [accessed on 8 Oct. 2014].

Moreover, the earlier the certificates issued, the more likely the certificates are subject to revocation by the review agency (**Fig. 1b**). For instance, among the certificates issued in 2003 for five main crops, 140 were revoked between 2008 and 2013, while only 71 revoked for those issued in 2004, 64 for those issued in 2005, 29 for those issued in 2006, 18 for those issued in 2007, nine for those issued in 2008, seven for those issued in 2009, and none since 2010 (see **Table 2**). The ratio of certificates issued in a given year being revoked later between 2008 and 2013 also showed trend of reduction since 2002 (**Fig. 1c**). Most of the nationwide popularization certificates being revoked were owned by Chinese domestic entities.

Table 2. Major crop varieties previously approved for nationwide popularization from 2001 to 2012 being revoked later (between 2008 and 2013)

Year of grant	Corn	Rice	Soybean	Wheat	Cotton	aggregate
2001	6	23	7	9	5	50
2002	1	0	0	0	4	5
2003	43	50	19	27	1	140
2004	19	32	5	13	2	71
2005	15	20	18	7	4	64
2006	10	10	6	2	1	29
2007	2	5	7	4	0	18
2008	1	3	3	2	0	9
2009	2	1	2	2	0	7
2010	0	0	0	0	0	0
2011	0	0	0	0	0	0
2012	0	0	0	0	0	0

Source: the data were compiled from various public notice issued by the Chinese Ministry of Agriculture, namely gonggao di 978 hao (24 Jan. 2008), di 1168 hao (24 Feb. 2009), di 1461 hao (19 Sep. 2010), di 1504 hao (13 Dec. 2010), di 1545 hao (17 Feb. 2011), di 1726 hao (14 Mar. 2012), di 2037 hao (18 Dec. 2013), guo pin shen [2013] 2 hao (20 Dec. 2013).

Table 3. Percentage of main crop varieties approved for nationwide popularization from 2001 to 2012 being revoked later (Revocation occurred between 2008 and 2013)

Year of grant	Corn	Rice	Soybean	Wheat	Cotton	aggregate
2001	46%	64%	58%	69%	100%	63.3%
2002	100%	---	---	---	80%	83.3%
2003	54%	57%	59%	60%	50%	56.9%
2004	41%	52%	71%	52%	67%	50%
2005	29%	34%	69%	32%	20%	36%
2006	15%	13%	21%	6%	6%	13.1%
2007	6%	10%	28%	13%	0	11.2%
2008	3%	7%	10%	10%	0	6%
2009	14%	2%	7%	6%	0	4.6%
2010	0	0	0	0	0	0
2011	0	0	0	0	0	0
2012	0	0	0	0	0	0

Source: the data were compiled from Table 1 and 2.

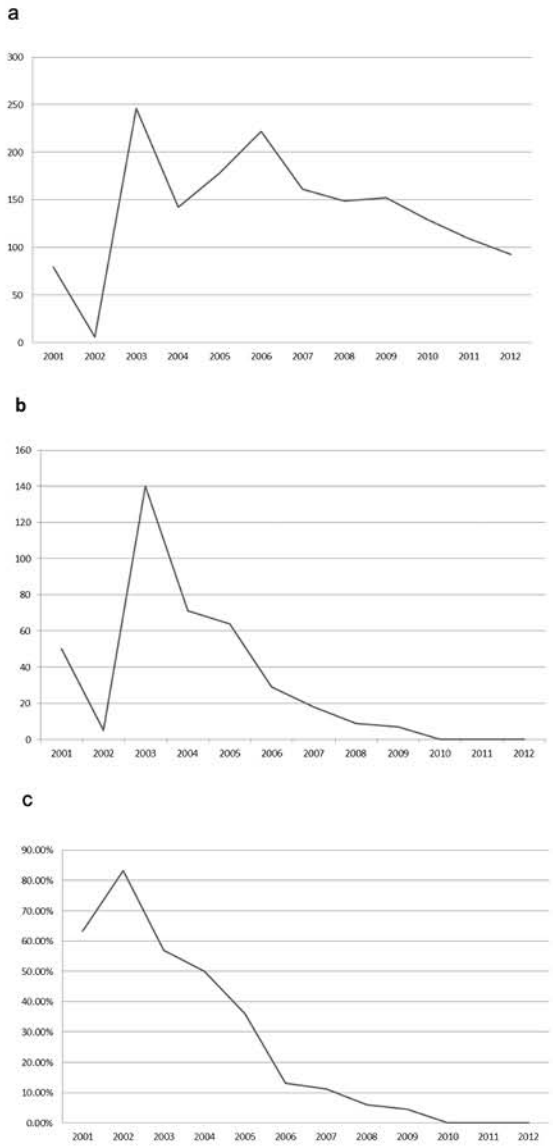

Figure 1. Certification of main crop varieties for nationwide popularization in China. (a) Number of certificates issued, 2001-2012. (b) Number of certificates issued from 2001 to 2012 being revoked. (c) Changing proportion of certificates issued from 2001 to 2012 being revoked. Source: see Table 1-3.

The exit mechanism, namely revocation of certification for nationwide popularization, has little effect on crop varieties owned by multinational companies, since the presence of multinational companies in the certification of crop varieties for nationwide popularization in China has been scant. As of 2013, only three crop varieties owned by multinational companies has been revoked for nationwide popularization. All three were corn varieties developed by Monsanto.[13, 16] On the other hand, a subsidiary of Pioneer-Hi Bred International still possesses seven valid certificates for corn varieties granted between 2004 and 2006.[10-12]

6. Implications for private investment

Multinational companies acquired very few certification of nationwide popularization for main crop varieties in China. Instead, multinational companies participated in the Chinese seed market as major importers of biotechnology crops. In 2008, the United States exported $8.4 billion USD soybeans to China and the vast majority were genetically modified varieties.[17] The disparity between multinational companies' direct participation in the Chinese seed market and indirect participation as a major importer of biotechnology crops is at least in part due to the different regulatory environment in China, as compared to the United States. So far, there is no sign showing that multinational companies would increase their direct participation in the certification for nationwide popularization of main crop varieties based on our data.

Accompanied with the heightened standard of review for nationwide popularization, the Chinese government also encourages vertical and horizontal integration of seed companies to strengthen their competitiveness, including the capability in research and development of outstanding new varieties. In other words, the Chinese government's policy is to enhance diversity, as opposed to plurality, of crop varieties in the market to cope with global competition as well as prospective climate or environmental change in the future.

Aside from China's newly adopted preventive measures and exit requirements, vertical integration from seed supply to sales is an alternative to assure seed quality if the legal institutions, such as seed certification or truth-in-labeling, are insufficient to address information asymmetries leading to farmers' inability to ascertain seed quality and source.[19, 22] Although China has a long history of policy promoting vertical integration in the agricultural sector since the 1990s,[23] among more than 6,000 domestic seed companies only 91 of them were capable of conducting vertical operations, including seed breeding, proliferation and marketing.[xxxiii] However, extensive merger and acquisition among seed companies are foreseeable as China's new policy continues.

The private sector's participation in the technological innovation in seed industry tends to be limited to seed technologies embedded in hybrids. The absence of public-sector participation may limit the R&D on crops and traits that the private sector has little interests, in particular rice and wheat. The potential for hybridization in rice and wheat is far less than for corn and cotton.[19] When a state-dominated seed industry transforms into privately-led seed industry, hybrid crops, such as corn and cotton, are among the most visible because hybrids provide private companies a greater ability to make a profit from cultivar improvement.[19] For instance, private investment in the research, development, and marketing of improved cultivars for rice and wheat in India has lagged that of cotton.[19]

Foreign varieties are likely facing much stiffer competition in larger countries with substantial domestic plant breeding capabilities,[20] such as China. The acquisition of

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xxxiii Staff reporter, 2014. Monsanto, Sinochem JV to become China's seed industry giant. Want China Times, 9 February 2014. <http://www.wantchinatimes.com/news-subclass-cnt.aspx?id=204029000057&cid=206> (accessed on October 2014).

xxxiv Staff reporter, 2014. Monsanto, Sinochem JV to become China's seed industry giant. Want China Times, 9 February 2014. <http://www.wantchinatimes.com/news-subclass-cnt.aspx?id=204029000057&cid=206> (accessed on 1 October 2014).

domestic seed companies give transnational companies possessing useful trait the access to locally adapted varieties, and then transfer the trait to a locally adapted variety to develop a new commercial variety.[20] Nonetheless, while industry consolidation through acquisition of a large number of domestic seed companies by transnational companies has been observed in Latin America and South East Asia,[7] as well as in India,[20] the same did not occur in China.

The Chinese government acknowledged that multinational companies' technologies are far ahead of Chinese seed companies, and the State Council encouraged the introduction of seed resources and advanced breeding technologies from foreign-owned companies.[21] On the other hand, the State Council was cautious about foreign-owned companies' activities in China, such as collecting seed resources, research, seed production and marketing, and the acquisition of Chinese companies.[21] Regulation on the activities of foreign-owned seed companies in China remains regardless of the reform.

However, in addition to mergers and acquisitions, market-based exchanges, technical collaborations, and joint ventures are also means that firms in developing countries to be part of innovation markets in the agriculture sector. For instance, most seed companies in India relied largely on licensing agreements to vertically integrate upstream research and development with downstream seed production and marketing, in particular in the Bt-cotton segment.[19]

Indeed, some multinational companies have established joint venture with Chinese seed companies. With the former's cutting-edge technology and the latter's quality-control system and after-sales service network, multinational companies were able to make further inroads into the Chinese market. In particular, Monsanto was previously confined in Guangxi province, which is in southern China. After establishing a joint venture with a Chinese company, it was able to extend its reach to the major maize production region in China, namely the northeastern and central part of the country.[xxxiv] The recent reform in China was expected to reduce customer confusion by excluding a large number of main crop varieties, which were previously granted, from the seed market. The government's determination on enforcing valid plant variety rights would increase the confidence and reduce the uncertainty for private investment. The Chinese government also encouraged merger, acquisition, and privatization in the seed sector to increase competitiveness. These measures were potentially beneficial for private investment in the seed industry, including investment from Hong Kong.

7. Conclusion

Since the State Council issued a broad-spectrum opinion in April 2011, the Chinese government has adopted numerous measures to redress the chaos and confusion in the seed market. Our study showed that a significant number of main crop varieties approved for nationwide popularization has been revoked in recent years. The number of certificates granted in recent years also showed a trend of decrease. The data showed that both the preventive measures and the exit mechanism have been effectively implemented as the State Council has instructed. These measures were potentially beneficial for private investment in the seed industry, including investment from Hong Kong.

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Chapter 13

REPOSITIONING HONG KONG'S BIOTECH INDUSTRY

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1. Review of Past Attempts and Obstacles

When the 1997 Asian Financial Crisis broke out following the handover of Hong Kong to China, the Hong Kong community experienced panic and felt insecure about the economy. As a major financial centre in Asia, Hong Kong suffered heavily from the regional capital outflow and the sharp reversal of bank lending. In light of the damages being exacerbated by the economy's excessive reliance on the financial sector, the Hong Kong Government decided to diversify the economy by promoting innovation and supporting technology-related industries by promoting the modernization of herbal medicines and supporting biotechnology and pharmaceutical-related healthcare industries. Many policy measures have been introduced since 1997 to serve the above purpose. Unfortunately, 20 years have passed and successful cases are rare. A comprehensive review of the attempts made by and the obstacles facing the local high-tech industry, such as biotechnology, is therefore required.

Since the beginning, the government has been aware of the importance of technology commercialisation. Such awareness could explain why the coverage of policy measures during 1997 – 2017 spanned from research funding, research institute establishment, office provision for biotech companies, subsidised facilities and equipment, incubation programs, to commercialisation support. Major policy measures included:

A. An annual spending of over HKD3 billion through the University Grant Committee (UGC) on basic scientific research conducted within local universities.

B. Setting up of the Innovation and Technology Fund (ITF) of HKD5 billion[1]. A number of programs supporting basic research, mid-stream research, and university-industry collaboration were under the ITF.

C. Private-sector venture capital firms were introduced to manage the Applied Research Fund (ARF) of HKD750 million[2]. The ARF aimed at supporting technology ventures or research projects undertaken by local companies.

D. Establishment of the Applied Science and Technology Research Institute (ASTRI), which focused on promoting mid-stream research in areas including health technologies[3].

E. Construction of the Hong Kong Science Park, providing office, subsidised biotech facilities and equipment, incubation programs, and commercialisation support[4].

F. Introduction of the Growth Enterprise Market (GEM) board. The GEM board provided a fund-raising venue for "high growth, high risk" businesses which might or might not fulfill the profitability record requirements on the main board of the Hong Kong Stock Exchange[5].

G. Establishment of the Innovation and Technology Bureau, which aimed at coordinating inter-bureau technology policies, encouraging private participation in scientific research, and promoting commercialisation of research outcomes[6, 7].

H. Introduction of overseas research institutions, including the Innovation Node of the Massachusetts Institute of Technology (MIT), the Karolinska Institute, and the Guangzhou Hong Kong Stem Cell and Regenerative Medicine Research Centre[8] The purpose of which is to enhance cooperation, and ultimately develop HK into a regional research hub.

Despite such diversified approach, biotech development appears to have remained stagnant for the past twenty years. Such failure might be attributed to a number of reasons.

First, overall spending on research and development (R&D) has remained relatively low. The city's annual R&D spending by percentage of GDP has been kept under 1% for the past twenty years[9], and has always been the lowest among the four Asian Dragons (Asian Dragons refer to Hong Kong, Singapore, Taiwan, and South Korea). By contrast, Singapore has raised its spending from 1.32% in 1996 to 2% in 2013[10]; South Korea has jumped from 2.24% in 1996 to 4.15% in 2013[11]. Since biotechnology requires huge investment and often takes more than ten years for commercialisation, it has been difficult for the local biotech industry to develop, given the low public and private investment.

Second, the policy measures have often relied too much on the academics. Professors in science and technology (S&T) were invited to chair think tanks, government

1 Hong Kong, Office of the Chief Executive, Chief Executive's Policy Address 1998, 10, accessed March 2017, http://www.policyaddress.gov.hk/pa98/english/epo/econ.pdf.
2 "Funding Schemes: Applied Research Fund," itc.gov.hk, last modified January 20, 2017, http://www.itc.gov.hk/en/funding/arf.htm.

committees, and technology institutions. While the purpose of those measures could be supporting technology ventures and promoting technology commercialisation, the people in charge of such measures might not have the required experience and expertise. Work involving technology ventures and technology commercialisation requires a comprehensive understanding of the concerning technology, the industry behind it, the regulatory framework in the area, the niche in the market, the knowledge on marketing and sales, etc. Since S&T professors might not have the expertise in doing so, policy measures should not rely too much on the academics. Instead, industrialists and people involved in technology management should be given more opportunities in policy making.

Third, there has been policy inconsistency over the past twenty years. Previous measures were often renewed, displaced, or even abandoned. For example, biotechnology was repeatedly emphasized by the government as a key developmental area during 1997 – 2001. However, after the establishment of the Biotechnology Research Institute (BRI) in 1999, biotechnology was removed as one of the thirteen focus areas in the public consultation paper "New Strategy of Innovation and Technology Development" in 2004[12]. Another example is the Applied Research Fund (ARF) being ceased without obvious reasons after the government transition in 2005. Also, the Hong Kong Jockey Club Institute of Chinese Medicine (HKJCICM), designated in 2001 to facilitate research upon traditional Chinese medicine (TCM) with modern biochemical knowledge, was disbanded without making any review on its failure in 2011[13]. Such examples clearly reflect policy inconsistency, which could discourage investment and participation in local biotechnology.

3 "About ASTRI: Corporate Information," astri.org, accessed March 2017, https://www.astri.org/about/corporate-info/.
4 Hong Kong, Office of the Chief Executive, Chief Executive's Policy Address 1998, 9, accessed March 2017, http://www.policyaddress.gov.hk/pa98/english/epo/econ.pdf.
5 "About GEM: The Market for Growth Enterprises," hkgem.com, accessed March 2017, http://www.hkgem.com/aboutgem/e_default.htm.
6 "Innovation and Technology Bureau: Our Role," itb.gov.hk, last modified November 2015, accessed March 2017, http://www.itb.gov.hk/en/about_us/role/.
7 Hong Kong, Office of the Chief Executive, Chief Executive's Policy Address 2014, 10-11, accessed March 2017, http://www.policyaddress.gov.hk/2014/eng/pdf/PA2014.pdf.
8 Hong Kong, Office of the Chief Executive, Chief Executive's Policy Address 2017, 15, accessed March 2017, http://www.policyaddress.gov.hk/2017/eng/pdf/PA2017.pdf.
9 Hong Kong, Census and Statistics Department, Research and Development (R&D) Expenditure by Performing Sector, last modified December 2016, accessed March 2017, http://www.censtatd.gov.hk/hkstat/sub/sp120.jsp?tableID=207&ID=0&productType=8.

Fourth, there has been no comprehensive review in spite of policy failures. The root causes to those failures have not been thoroughly investigated, therefore follow-up corrective measures could not be established. Failures can take different forms. In a 2005 research titled "Innovation Policy Forensics: An Analysis of Biotechnology in Hong Kong", Professor Erik Baark from the Hong Kong University of Science and Technology (HKUST) used the Hong Kong Institute of Biotechnology (HKIB) as a case to explain the different types of policy failure[14]. The HKIB was established in 1988 for stimulating local biotech R&D and providing the essential infrastructure in this regard. However, as Baark illustrated, the HKIB initiative had become a market failure due to the government's misunderstanding about the market. It had become a systemic failure as it had failed to address the needs of the local pharmaceutical industry; and that it had become a learning failure because of the government's reluctance to perform follow-up evaluation and adaptations. The case illustrated the need for comprehensive review following policy failures. Unfortunately, the government has chosen to ignore such failures while continuing to develop new policy initiatives without changing its policy approach from the past failures.

Fifth, research findings have not been successfully developed into commercial products. Local universities, including the Hong Kong University (HKU) and the Hong Kong University of Science and Technology (HKUST), have been yielding research findings that are internationally-recognised. However, the high-quality research has not been successfully developed into commercial products. This is sometimes referred as the "Big R and Small D Syndrome[15] ". Since commercialisation has been unsuccessful, the findings generated by expensive yet high-quality research cannot in return contribute to the local biotech industry.

10 United Nations Educational, Scientific, and Cultural Organization (UNESCO) Institute for Statistics, Research and development expenditure (% of GDP), accessed March 2017, http://data.worldbank.org/indicator/GB.XPD.RSDV.GD.ZS.
11 United Nations Educational, Scientific, and Cultural Organization (UNESCO) Institute for Statistics, Research and development expenditure (% of GDP), accessed March 2017, http://data.worldbank.org/indicator/GB.XPD.RSDV.GD.ZS.
12 Innovation and Technology Commission, Consultation Paper: New Strategy of Innovation and Technology Development (Hong Kong: Innovation and Technology Commission, 2004), ch. 19, accessed March 2017, http://www.itc.gov.hk/en/doc/consultation/consultation_paper_e.pdf.
13 The Government of the Hong Kong Special Administrative Region, "LCQ11: Hong Kong Jockey Club Institute of Chinese Medicine," news release, October 2011, accessed March 2017, http://www.info.gov.hk/gia/general/201110/26/P201110260306.htm.

Sixth, outflow of science and technology (S&T) talents to overseas areas has weakened local biotech development. Top S&T graduates among local universities have shown a strong tendency to pursue further studies or build their own companies overseas. Although they could be returning to HK in the future, many would choose to settle and work there because of the better research environment or stronger support for technology companies. With fewer S&T talents in HK, the local biotech industry might be unable to compete with other countries and regions.

As can be seen from the above analysis, attempts have been made by both the government and the industry but obstacles facing local biotech development still remain. From an industrial perspective, the situation cannot be reversed without improving the R&D spending, the society's understanding of the local technology environment, the constituents and consistency of policy, the review on policy failure, the commercialisation capability, and the ability to retain science and technology (S&T) talents. However, from an entrepreneurial perspective, a lot can be done within the company in order to increase the chance of survival and eventually succeed. The following section discusses the critical factors behind a successful high-tech business such as a biotech venture, and the pros and cons of starting the business in Hong Kong.

14 Erik Baark, "Innovation Policy Forensics: An Analysis of Biotechnology in Hong Kong," 23-24, June 2005, accessed March 2017, http://www.druid.dk/uploads/tx_picturedb/ds2005-1557.pdf.

15 Perry S.O. Chan and Chi-Ming Lee, "Fostering the Growth of Biotech Industry in Hong Kong - With a Focus on Personalized Medicine," in Biotechnology in Hong Kong, vol. 2 (New York: United States-China Intellectual Property Institute Inc., 2015), 117-53.

2. Developing a Path for Local Biotech Companies – A Corporate Perspective

2.1 The Critical Factors behind a Successful Biotech Company

The critical factors governing the success and failure of a biotech company can be broadly categorised into two groups – extrinsic factors and intrinsic factors (Figure 1).

Figure 1. Critical factors governing the success and failure of a biotech company. Most factors are either extrinsic (i.e. uncontrollable by a company) or intrinsic (controllable within a company). Government is, however, a special factor spanning both categories.

2.1.1 Extrinsic Factors

Extrinsic factors include the global environment, the specific industrial environment, the international and regional regulation, the market demand, and the local government's technology policy.

The global environment includes many geographic factors that give global, regional, local, and cluster effects. In addition, each geographic factor can be evaluated based on various sub-factors, such as socio-cultural, technological, economic, political, ecological, legal, environmental/ethical, education, demographics, etc. Most factors are not controllable by individual company. However, they must be carefully evaluated

prior to a business launch. The tools to evaluate such factors are reported by various investigators such as SWOT, STEEP, STEEPLE, and PEST. Details of such analyses are summarized briefly on the website titled Pestle Analysis[16].

Another extrinsic factor is the specific industrial environment. It includes many sub-factors relating to an individual entity's position within an ecosystem of value chains and supply chains. By analysing the relative position of an individual company within the processes of value organization and industrial-chain-structure creation, one can raise the influential and competitive power of the company based upon the resulting information[17].

Other extrinsic factors include the international and regional regulation, the market demand, and the local government's technology policy. For the past twenty years, there has been a trend for biotechnology to develop into more convenient, accurate, and rapid solutions. An example is bio-testing technology.

Bio-testing technology leverages living organisms, biological parts, tissues, embryos, or body cells to test for specific chemicals in a particular environment. As public awareness over food, product, and environmental safety grew in recent years, bio-testing has become another hot topic. An example of bio-testing is the Medaka Embryo Test for estrogenic endocrine-disrupting chemicals (CEEDs) provided by the HK-based company Vitargent (International) Biotechnology Limited[18]. Estrogen is a sex hormone responsible for the development and regulation of female sex characteristics[19]. CEEDs disrupt the estrogen level, causing abnormal body development during puberty, or even changing the onset of puberty. The medaka embryos are modified with jellyfish DNA so that they would glow upon exposure to CEEDs[20]. The test can be widely applied to identify CEED-containing food, cosmetics, clothing, etc.

16 "Difference between SWOT, PEST, STEEP and STEEPLE Analysis," Pestle Analysis, February 2015, accessed April 2017, http://pestleanalysis.com/difference-swot-pest-steep-steeple-analysis/.

17 Michael E. Porter, Competitive Advantage: Creating and Sustaining Superior Performance (New York: Simon and Schuster, 1985).

18 "How we test: Medaka," vitargent.com, accessed March 2017, http://www.vitargent.com/technology/.

19 "CHEBI:50114 - estrogen," ebi.ac.uk, last modified March 2017, , accessed March 2017, http://www.ebi.ac.uk/chebi/searchId.do?chebiId=50114.

20 "How we test: Medaka," vitargent.com, accessed March 2017, http://www.vitargent.com/technology/.

Despite having a novel technology with wide application, Vitargent was still subjected to extrinsic factors including the international and regional regulation, the market demand, and the local government's technology policy. The case therefore is not only a technological breakthrough, but also an illustration of how a biotech company handles regulation, addresses market demand, and benefits from local technology policy. The test was developed with early-stage medaka embryos, which are not regarded as animals under the European Union (EU) regulations. The technology therefore would not violate several EU regulations against animal testing, and could enter the EU market smoothly. When it came to the company launch, Vitargent chose the Hong Kong Science and Technology Park (HKSTP) as its base. This allowed easy access to the growing demand for food safety testing in China. The company also benefited from local technology policy, such as the incubation programs within the HKSTP. Marketing and financial support were given to the incubatees.

A biotech venture should be able to leverage the extrinsic factors to its own benefits. As can be seen from the above example, sufficient understanding and proper responses towards the global trend of biotechnology, the international and regional regulation, the market demand, and the local government's technology policy are necessary in order for a biotech company to succeed.

2.1.2 Intrinsic Factors

Intrinsic factors determine whether a biotech company can successfully plan, execute, improve, and expand its businesses. Three major intrinsic elements are technology, funding, and people (i.e. leaders, leadership, together with an effective and highly-inclusive team) with a clearly-articulated execution plan. The intrinsic elements are totally controllable within the company. The three elements form the classical Golden Triangle of Business (Figure 2). Combining with proper business management, timely decision making, and strong teamwork, success can be achieved. Understanding the three elements and mastering the underlying operating principles can eliminate most hurdles along the development of a high-tech company.

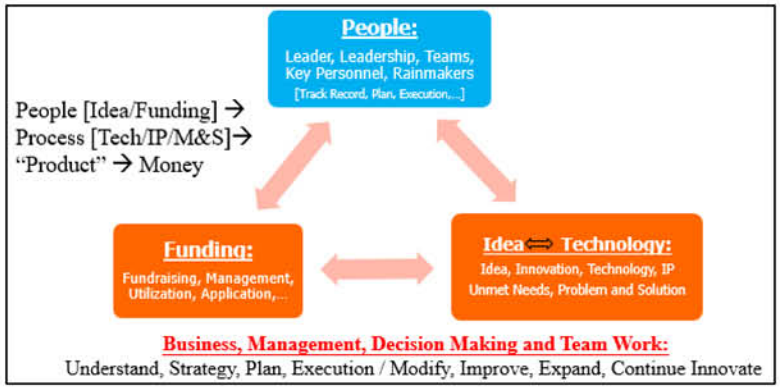

Figure 2. The classical Golden Triangle of Business. The triangle is formed by three elements – technology, funding, and people. It functions the best when combined with proper business management, timely decision making, and strong teamwork.

2.1.2.1 Technology

Technology can be the foundation of a biotech company. Proper technology planning is therefore necessary. Generally, the planning should cover four key steps – identifying the primary usage, confirming the current developmental stage, targeting particular markets, and revealing the core technology contribution[21]. Using the previously-mentioned Medaka Embryo Test as an example, the primary usage was identified to be the detection of estrogenic endocrine-disrupting chemicals (CEEDs). Medaka embryos might be genetically modified to detect other substances such as heavy metals, but such option had not been adopted. The test was developed from a working-hypothesis stage, when it was still a university research project. It attempted to fill the market niche for a faster, more economical test with wider application compared to traditional chemical tests. Its core technology contribution lied in the modifications of the medaka embryo's genome, and the application of such modifications for the detection of CEEDs.

While making a technology plan, it is also important to consider the patentability of the technology concerned and the public expectation upon it. A technology must satisfy four criteria – novelty, non-obviousness, enablement, and utility – in order to get patented[22]. It is common for a new technology to be based upon existing ones. In this case, its core technology contribution should be well-defined and should not infringe existing patents. In addition to patentability, the technology also needs to fulfil the public expectation. For instance, medical biotechnology is generally expected to be safe, to have high efficacy, and to show consistent quality[23].

2.1.2.2 Funding

Funding serves as the fuel for a biotech company but can fluctuate as the company goes through different stages of the business life cycle. Prior to funding a biotech company, investors would want to know the current and expected values of the proposed technology, the timing for selling or licensing out the technology in order to gain the maximum profits, the company track record and past accomplishments, and the existing investor composition. All these could help the investors assess the risks, costs, and possible returns from an investment; and should be provided by the company if it is seeking funding.

21 Kwei-hang Chan and Yi-chen Su, Theory and Practice on Technology Commercialization (Taipei: 華泰文化), 13-16.
22 Kwei-hang Chan and Yi-chen Su, Theory and Practice on Technology Commercialization (Taipei: 華泰文化), 4.
23 Kwei-hang Chan and Yi-chen Su, Theory and Practice on Technology Commercialization (Taipei: 華泰文化), 4.

As a company goes through different stages of the business life cycle, it would have varying financial needs and funding opportunities. In general, there are seven developmental stages – seed, start-up, growth, established, expansion, mature, transformation or exit[24]. Here we use two of them as examples for illustrating the varying financial needs and funding opportunities.

Seed stage refers to the time when the company has just been set up. During this period, the company does not have any proven markets or customers. Therefore it is less likely to attract veteran investors who value company track record and past accomplishments. Funding could, however, come from government grants, angel investors, or the owners themselves. In order to survive, the company has to make a good evaluation of the cash need for the upcoming months. As the year passes by, it would also need a future-year plan for convincing new shareholders to support the next phase of development[25].

Growth stage refers to the period when the company starts running the business in a more formal manner amid increased customers and sales. The market competition gets more intense but the profits keep rising. Labour cost could increase as more employees are needed to manage the growing business. Similarly, overhead expenses including rents, utilities, and insurance could increase in order to meet the demand. While financial needs could be rising, there would be new funding opportunities. Since the company now has proven markets and customers, it is more likely to get funding from professional investors. Not only can the company rely upon its own profits, but also get funding through venture capitalists, banks, or partnership with other companies[26].

As can be seen, a company would have varying financial needs and funding opportunities when it goes through the business life cycle. Biotech companies should know what investors are seeking during the various stages, and capture the respective funding opportunities.

2.1.2.3 People

People form the core of the company, which are responsible for all the planning and execution. The initial team should consist of highly-motivated individuals who are able to understand, strategize, plan, and execute their innovations. The entrepreneur should lead by creating an atmosphere where innovative solutions are encouraged and teamwork is encouraged. As the company grows, interdisciplinary talents can be recruited to facilitate reassessment of the original business plan, raising funds, redesigning the company structure, and promoting technology commercialisation. It is also worth pointing out that different talents would be needed during the various developmental stages. The entrepreneur and his team would have to learn, adjust, improve, and expand throughout the business life cycle. Here we again use the seed stage and growth stage as examples to illustrate the above notions.

Seed stage is fundamentally a planning stage. The most important task at this stage is to create a comprehensive and operable business plan. If the biotech company starts with science and technology (S&T) professionals who are not familiar with business planning, outside advisors experienced in start-up management could be introduced to the board. The opposite – where the company begins with business professionals – could also occur. In that case, S&T professionals should be recruited instead. Other important tasks include making a good evaluation of the cash need for the upcoming months, and developing a future-year plan for convincing new shareholders to support the next phase of development. The former requires financial analysts, whereas the later requires visionary managers with assiduity and flexibility in order to keep the business model in line with rapid market evolution[27].

Growth stage is when the company gets challenged by and has to adapt to increased customers and sales. Since time and resources are both limited, the company would need experienced managers to prioritise the wide range of work. To deal with the wide range of work, the company might need to improve its productivity by such means as automation, licensing out, or outsourcing certain work to a third party. There might also be the need to redesign the company structure, such as assigning people specifically for management, accounting, and marketing. Meanwhile, the process of technology commercialisation would have to be sped up. This would require interdisciplinary talents who understand two or more among the following: technology, intellectual property, regulatory standards, finance, marketing, or competitive analysis. Besides, rainmakers or venture capitalists can be introduced to the board at this stage. Not only can they bring in new funding, but also open up more opportunities for partnerships and gaining new customer segments[28].

24 Thierry Janssen, "The 7 stages of business life cycle," editorial, accessed March 2017, http://www.justintimemanagement.com/en/The-7-stages-of-business-life-cycle.
25 Thierry Janssen, "The 7 stages of business life cycle," editorial, accessed March 2017, http://www.justintimemanagement.com/en/The-7-stages-of-business-life-cycle.
26 Thierry Janssen, "The 7 stages of business life cycle," editorial, accessed March 2017, http://www.justintimemanagement.com/en/The-7-stages-of-business-life-cycle.

2.1.3 The Special Factor – Government

The government is a special factor which can influence the many extrinsic factors (i.e. the global environment, the specific industrial environment, the international and regional regulation, the market demand, and the local government's technology policy). To be more specific, the government can for example provide a business environment favourable to start-ups; subsidize technologies which have spill-over effects on the economy; influence or even reshape particular markets (e.g. creating a market for carbon emission trading); and roll out policies that encourage technological innovations. In order to evaluate the past attempts of the Hong Kong Government in promoting innovation and supporting technology-related industries, a table has been made (Table 1).

27 Thierry Janssen, "The 7 stages of business life cycle," editorial, accessed March 2017, http://www.justintimemanagement.com/en/The-7-stages-of-business-life-cycle.

28 Thierry Janssen, "The 7 stages of business life cycle," accessed March 2017, http://www.justintimemanagement.com/en/The-7-stages-of-business-life-cycle.

Table 1. Past attempts of the Hong Kong Government in promoting innovation and supporting technology-related industries.

Criterion / Factor	✓ - The government succeeded in this criterion / factor × - The government failed in this criterion / factor ? – The government made its attempt(s) in this criterion / factor but the outcome was questionable	Explanation / Example(s)
Supporting scientific research through public institutions and funding	✓	• Applied Science and Technology Research Institute (ASTRI) • Funding through the University Grant Committee (UGC)
Supporting commercialisation of research outcomes	?	• Commercialisation ability has remained weak despite initiatives such as the Innovation and Technology Fund (ITF)
Providing a business environment favourable to technology start-ups	✓	• Hong Kong Science and Technology Park (HKSTP) • Growth Enterprise Board (GEM)
Technology policies are developed across disciplines – academics, industrialists, and small businesses are equally consulted	×	• Has relied too much on the academics
Technology policies are kept consistent over the years	×	• Applied Research Fund (ARF) was ceased without obvious reasons
Review following policy failures	×	• Hong Kong Institute of Biotechnology (HKIB) has not been reviewed despite its failure • Hong Kong Jockey Club Institute of Chinese Medicine (HKJCICM) was disbanded without follow-up review
Retaining science and technology (S&T) talents in HK	×	• Outflow of S&T talents to other countries and regions

As can be seen from Table 1, the government has attempted to support research, promote commercialisation, and provide a business environment favourable to technology start-ups. However, the means by which the government has used appear to be very narrow – limited mainly to funding. When the technology policies are examined in more detail, it is obvious that the government has been unable to offer a comprehensive set of policies to issue. Besides, the incomplete, narrow policies rolled out by the government could not be sustained for a long period of time. Also, policies in other areas have not been coordinated with the technology policies. For example, there seems to be a mismatch between the education policies and the technology policies, resulting in science and technology (S&T) graduates going to other countries or regions in pursuit of better career opportunities. All these problems must be properly addressed in order to boost the government's stagnant performance in promoting innovation and supporting technology-related industries.

2.2 The Pros and Cons of Starting a Biotech Company in HK

Launching the business in HK has both pros and cons. Local biotech companies should not rely too much on government support, because the policy might change from time to time as discussed earlier. As a major financial centre in Asia, fund-raising is supposed to be easier than the nearby regions. However, the continually-inflating property and stock markets are often preferred to the "high growth, high risk" businesses when it comes to investment. Such preference could deter investment upon biotech companies.

When it comes to local talents, HK has abundant professionals in biomedical sciences, finance, intellectual property protection, and corporate management. Despite that, HK has been very weak in transforming knowledge into commercial products or services. This is not only because of the "Big R and Small D Syndrome", where high-quality research at university fails to contribute to the local industry[29]; but also due to the lack of interdisciplinary talents with global vision. Nowadays, the value chain of a biotech company could span across the Pacific and other oceans in order to get the maximum value added with the least total cost. Research and development (R&D) could be carried out in the U.S., whereas mass production and global marketing could be done in China and HK respectively. Innovation, regardless of whether it is radical or incremental in nature, could occur at any stages. Interdisciplinary talents with global vision, for example people who understand both the manufacturing process and the regional safety requirements for biotech imports, are much needed in order to improve the processes, products, or services. Without them, innovation can hardly occur.

When it comes to corporate environment, the cost of failure is very high in HK. Generally, the survival rate for small businesses is only 12% within the first five years, and only 2.4% within the first ten years[30]. Since the operational costs from rent, salary, utility, insurance, etc. are high in HK, the initial investment for a local start-up must be high. If failure occurs, the subsequent loss would thus be very high. Such conditions have deterred investments and participation in biotech companies. Even after establishment, some local biotech firms are still reluctant to provide incentives such as employee stock options (ESOs) in fear of the subsequent costs; despite knowing that they could promote a sense of belonging towards the company and encourage contributions.

Despite the above setbacks, HK has the foundation for supporting biotech companies and has made new attempts to facilitate their development. In order to address the lack of interdisciplinary talents, various local universities have begun to offer degrees spanning science, technology, and business. The Hong Kong University of Science and Technology (HKUST) is the first local university to offer such degrees. Its dual degree program in biotechnology and general business management aims not only at delivering knowledge in both areas, but also coaching students on their way to starting a company. Another example is the City University of Hong Kong (CityU), which offers the dual degree program in e-logistics and technology management. A graduate of this program, Mr. Eric Chen, is the founder of the firm Vitargent (International) Biotechnology Limited discussed earlier.

As a successful biotech spinoff from a local university, Vitargent (International) Biotechnology Limited might offer some insights of running the business here. Its renowned Medaka Embryo Test for estrogenic endocrine-disrupting chemicals (CEEDs) was originally a research project under the Department of Biomedical Sciences at the CityU[31]. The project was led by two scientists - Prof. Cheng Shukhan and Dr. Xueping

29 Perry S.O. Chan and Chi-Ming Lee, "Fostering the Growth of Biotech Industry in Hong Kong - With a Focus on Personalized Medicine," in Biotechnology in Hong Kong, vol. 2 (New York: United States-China Intellectual Property Institute Inc., 2015), 117-53.

30 Thierry Janssen, "The 7 stages of business life cycle," accessed March 2017, http://www.justintimemanagement.com/en/The-7-stages-of-business-life-cycle.

31 Christina Wu, "Alumni win top international award with biotech invention," CityU NewsCentre, last modified April 2015, accessed March 2017, http://wikisites.cityu.edu.hk/sites/newscentre/en/pages/201504211800.aspx.

Chen. As a student of Prof. Cheng, Mr. Chen developed a business proposal for the project; which eventually became Vitargent. Vitargent then received the exclusive licenses for using the research findings from the CityU. Meanwhile, Prof. Cheng and Dr. Chen became the advisor and chief technology officer (CTO) of the company respectively. In 2015, Vitargent completed A Round financing led by WI Harper Group, a renowned venture capital firm (A Round financing refers to the first major round of business financing either by private equity investors or venture capitalists)[32]. Having access to the board, WI Harper Group announced in the same year that it would promote the company's bio-testing services to governments and industrialists around the globe.

The case of Vitargent shows that HK is indeed capable of generating successful biotech companies. The lack of interdisciplinary talents could be addressed and is expected to be solved following the introduction of degrees spanning science, technology, and business. As a major financial centre in Asia, HK can offer enormous fund-raising opportunities for biotech companies with a good business plan. WI Harper Group is only one among the many venture capital firms operating in the city. In addition, launching a company here can enjoy the protection of common law and a low tax regime. HK also has a good geopolitical position, acting as the trading hub for large economies including China, Japan, and Indonesia. If one is able to locate and fulfil any existing market niches in the region, for example the growing demand for food safety testing in China as in the case of Vitargent, the chance of succeeding would be even greater.

3. Suggestions to Local Biotech Companies

Local biotech companies need to have sufficient understanding over the global trend of biotechnology, the international and regional regulation, the market demand, and the local government's technology policy in order to give proper responses amid intense market competition. In addition, they should have the right technology, funding, and people in order to achieve their business goals. Choosing the right technology takes four key steps - identifying the primary usage, confirming the current developmental stage, targeting particular markets, and revealing the core technology contribution. Other aspects such as patentability and public expectation should also be considered. Financial needs and funding opportunities change as the company develops. At the beginning, funding opportunities might be minimal but could still come from government grants, angel investors, or the owners themselves. Good evaluation of the cash need would be essential at this stage. As the company develops, the financial needs due to rising labour cost and overhead expenses would increase. However, there could be new funding opportunities through venture capitalists, banks, or partnerships with other firms. In order to grasp the various opportunities and avoid the obstacles, a highly-motivated team which can understand, strategize, plan, and execute their innovations should be formed. During the early stages, outside advisors who are familiar either with technology or start-up management could be introduced to the board. Financial analysts capable of evaluating the cash need and developing a future-year plan, as well as visionary managers with the assiduity and flexibility to stay in line with rapid market evolution, should be gathered. As the business grows, experienced managers, professionals in technology commercialisation, and rainmakers could be introduced in order to prioritise the work, speed up the process of commercialisation, bring in new funding, create more opportunities for partnerships, and explore new customer segments.

While leveraging both the extrinsic and intrinsic factors could boost the chance of success, it is also important for entrepreneurs to learn that their businesses could be of any natures and could target any stages of the business life cycle. The overwhelming notion that biotech businesses should rely upon investigational new drug (IND) development could prevent companies from succeeding by providing other products

32 "HK-Based Bio Tech Startup Vitargent Closed Series A Round," EntrepreneurHK (EHK), accessed March 2017, http://entrepreneurhk.org/hk-based-bio-tech-startup-vitargent-closed-series-a-round/.

or services. Examples of such products or services include sourcing global suppliers for particular raw materials, collecting clinical samples, providing good laboratory practice (GLP) facilities, distributing the finished products around the globe, patenting of new technologies, licensing technologies to a third party, and providing exit strategies such as initial public offering (IPO). Even starting a franchise, such as running a GLP facility with the business model and brand name of an established provider, can be an option. In fact, the overall success rate for a drug to get from discovery through pre-clinical, IND, and clinical phases to final approval by the U.S. Food and Drug Administration (FDA) is only 0.000035%[33]. Drug development therefore should not be the focus of every biotech company, especially not for those without stable and long-term sources of funding. On the other hand, entering the market as a franchise could be an advantage. This is because the survival rate for small businesses without franchise is very small, only at 12% within the first five years; and at 2.4% within the first ten years. However, the number could be largely increased to 60-70% if one enters the market as a franchise[34]. This is because t he business model and critical process have been proven to work. Therefore, commercialization strategy of a technology should not be overlooked during technology commercialization. The principle of franchising that allowing the one who knows the business and process to help could serve as a better pathway for new entrants. As can be seen, biotech companies should not refrain from engaging in products or services other than IND development. Hong Kong should leverage its expertise in business process to develop its biotechnology industry.

33 Michael Hay et al., "Clinical development success rates for investigational drugs," Nature Biotechnology 32, no. 1 (2014): 40-51, doi:10.1038/nbt.2786.

34 Thierry Janssen, "The 7 stages of business life cycle," accessed March 2017, http://www.justintimemanagement.com/en/The-7-stages-of-business-life-cycle.

4. Conclusion – Leveraging the Competitive Edge of HK

HK's competitive edge lies within its vibrant and free economy, reliable common law system, low tax regime, close proximity to large economies such as China, high-quality scientific education and research at local universities, and a considerably-large talent pool for disciplines such as corporate management. All three elements forming the classical Golden Triangle of Business – technology, funding, and people – can be found in HK. Also, the case of the HK-based company Vitargent (International) Biotechnology Limited has proven that HK is capable of generating successful biotech companies.

A biotech company should be able to leverage the above extrinsic and intrinsic factors to its own benefits. In addition, it should have sufficient understanding of and proper responses towards the global environment, the specific environment of its industry, the international and regional regulation, the market demand, and the local government's technology policy. It is also for the company to learn that their business could be of any natures and could target any stages of the business life cycle. Possible modes of business include investigational new drug (IND) development, sourcing global suppliers for particular raw materials, collecting clinical samples, providing good laboratory practice (GLP) facilities, distributing the finished products around the globe, patenting of new technologies, licensing technologies to a third party, providing exit strategies such as initial public offering (IPO) and even starting a franchise with the business model and brand name of an established company. Biotech companies should not refrain from engaging in products and services other than IND development.

However, there are certain areas in which HK has been performing poorly and should be addressed by both the government and the industry. First, HK has been very weak in transforming knowledge into commercial products or services. This is partly because of the "Big R and Small D Syndrome", where high-quality research at university fails to contribute to the local industry; and partly due to the lack of interdisciplinary talents with global vision to carry out process, product, or service innovation. The problem can be corrected by enhancing university-industry collaboration (in order to enhance commercialisation of research outcomes), offering degrees spanning science, technology, and business (which the government has already started doing), and recruiting local S&T talents who have gone overseas back to HK (through jobs or start-up opportunities). Second, the cost of failure from starting a business is high in HK. Since the operational costs from rent, salary, utility, insurance, etc. are high in HK, the initial investment for a local start-up must be high. If failure occurs, the subsequent loss would thus be very high. Such conditions have deterred investments and

participation in biotech companies. To remove this obstacle, the government could consider expanding its incubation programs for technology start-ups. For example, the period of tax reduction for the incubatees could be extended; while support in marketing, finance, and management for highly-potential firms could continue beyond the incubation period. Third, the government has been unable to develop a comprehensive set of policies for promoting innovation and supporting technology-related industries. To correct this, the government must agree on reviewing its own policy failures. The review can either be done by the government itself, or by a third-party policy consultant. Only after the review would the government be able to learn from its own failures and develop a comprehensive set of policies.

After making improvements in the above criteria, HK's competitive edge in launching a high-tech company such as biotechnology would be even greater. Companies would thrive as they choose HK as their base.

Chapter 14

HONG KONG PATENT SYSTEM: UNIQUE FEATURES FOR GLOBAL IP STRATEGY

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INTRODUCTION

Since Hong Kong opened for trade in 1842, it has always assumed a unique position serving as a bridge between the western world and China. After the handover in 1997, Hong Kong has retained the common law system used since its colonial days and continued to prosper as an international financial center. As China attempts to shift from being simply the "World's Factory" to high-end product manufacturing, Hong Kong is expected to continue its role and contribute to this transformation. Despite being a developed economy, Hong Kong was seldom associated with high-tech and innovation. In fact, the general public in Hong Kong has a rather negative perception on high technology investments, which the government is trying hard to change[1]. Cornell University, INSEAD and WIPO co-publish the Global Innovation Index (GII) which evaluates and ranks countries based on 82 indicators by their capacity for, and success in, innovation. Surprisingly, Hong Kong has been consistently ranked as one of the most innovative economies on a global level (See TABLE 1) [2,3,4,5]. Careful examination of the GII shows that Hong Kong has a very high innovation input sub-index ranking but a relatively low output sub-index ranking. The input sub-index reflects the elements of the economy that enable innovative activities while the output sub-index are the results of innovative activities. In other words, Hong Kong has a fertile ground for innovation that has not been fully utilized. In this article, we will examine some of the unique features of the Hong Kong patent system that may be attractive to innovators and investors interested in the high tech industries.

Table 1. GII and Sub-indices of Hong Kong in 2013 to 2016

Year	Global Innovation Index*	Innovation Output Sub-Index	Innovation Input Sub-Index
2016	14	25	2
2015	11	19	4
2014	10	24	2
2013	7	15	2

*Ranks out of 142, 143, 141 and 128 in 2013 to 2016 respectively

PATENT LAW BASICS

The Patent Ordinance (Cap. 514) enacted in June 1997 provides two forms of patent protection in Hong Kong:

1) Standard Patent (20 years patent term);
2) Short-term Patent (8 years patent term).

The application process for each of the two patents are shown in FIGURES 1A and 1B. In brief, the standard patent extends any patent rights granted on a designated patent in one of the following three "designated patent offices":

i. the State Intellectual Property Office, People's Republic of China;

ii. the European Patent Office, in respect of a patent designating the United Kingdom; and

iii. the United Kingdom Patent Office.

iv. The Hong Kong Intellectual Property Department (HKIPD) will only conduct a formality check on documents submitted when applicant makes a request to record (stage 1) and a request for registration and grant (stage 2). Patentability of the invention is relied solely upon on the work product of the designated patent offices.

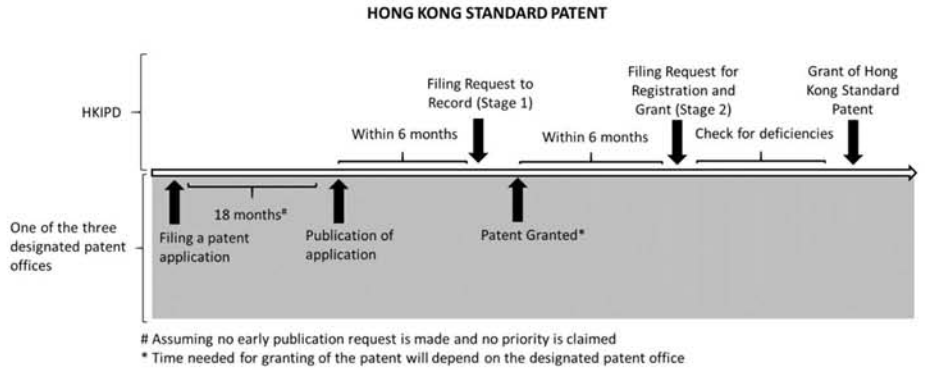

FIGURE 1A. Application Process for Standard Patent

For short-term patent, the IPD will only examine on the application documents on formality issues but a search report issued by one of the three designated patent offices or an international searching authority (ISA) need to be submitted. The search report will contain the opinion from an Examiner on the patentability of the invention based on cited references obtained in a prior art search.

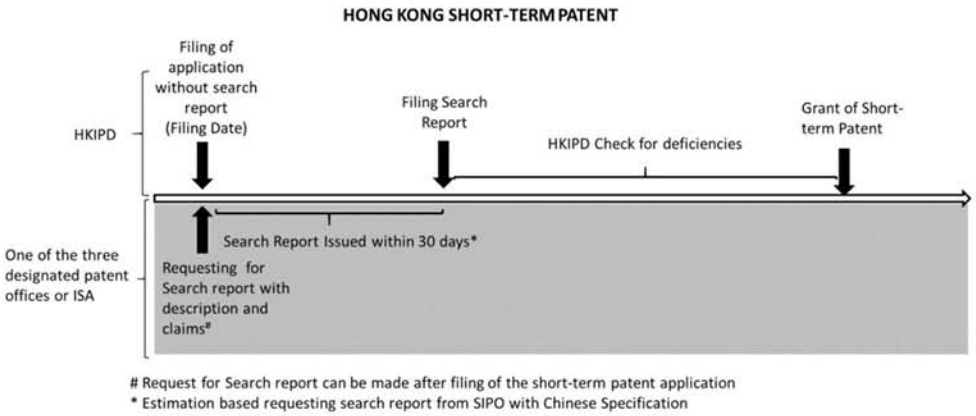

FIGURE 1B. Application Process for Short-term Patent

The number of standard patents and short-term patents filed in Hong Kong per year are shown in TABLE 2 [6,7]. In comparison with Singapore, which can be considered an economy of about the same size, the number of patent applications filed and granted each year in Hong Kong seems to be reasonable [8].

Table 2. Hong Kong Patent Statistics

Year	Standard Patent		Short-term Patent	
	Filed	Granted	Filed	Granted
2016	14092	5698	762	485
2015	12212	5963	702	495
2014	12542	5932	587	522
2013	13916	6564	552	538
2012	12988	5035	645	515

*Statistics from Intellectual Property Office of Singapore:
Patents filed in 2012-2014 are 9685, 9722 and 10312 respectively
Patents granted in 2012-2014 are 5633, 5575 and 5538 respectively

With the Legislative council passing the Patent (Amendment Bill) 2015 in June 2016, a third form of patent, known as the original grant patent (OGP), is expected to come into effect in 2018 [9]. OGP would be the first form of patent whereby substantive examination of patentability will be carried out locally. Whether this will present new opportunities for Hong Kong remains unknown until the OGP is implemented.

Selected features of the current Hong Kong patent ordinance which help local high-tech companies in the race against worldwide competition are discussed below.

STANDARD PATENT

The Hong Kong standard patent is essentially an extension of an issued patent right in China or UK to Hong Kong. With this in mind, one will not be surprised that the Hong Kong patent law has to accommodate the differences between China and UK patent law. This feature may be attractive to technologies where patent protection is a key factor for its success. Biotechnology, such as pharmaceutical drugs, often involves a long development process and faces a huge regulatory hurdle which must be funded by a large amount of investment. By being able to claim exclusive rights, patent protection offers a way for recouping these investments made in the pre-market stage and provides a driving force for progress of biotechnology. On the other hand, it is highly debated whether the law should provide exclusive right protection to biotechnology which raises moral issues such as manipulation of living organism.

According to the United Nations Convention on Biological Diversity[10], "biotechnology" is broadly defined as:

> *"any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use."*

As an example to illustrate the Hong Kong patent system, the following discussion will be limited to patenting inventions that involves the use of human embryonic stem cell (hESC) which is one of the most highly debated issues in the biotechnological field. In general, hESC are rejected as moral exclusions. The relevant law in the three jurisdictions are recited as follows:

[European] EPC Article 53(a):

> *"inventions the commercial exploitation of which would be contrary to "ordre public" or morality; such exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation in some or all of the Contracting States; "*

Chinese Patent Law Article 5:

> *"Patent rights shall not be granted for invention-creations that violate the law or social ethics, or harm public interests. Patent rights shall not be granted for inventions that are accomplished by relying on genetic resources which are obtained or used in violation of the provisions of laws and administrative regulations."*

Hong Kong Patent Ordinance Section 93 (5):

> *"An invention the publication or working of which would be contrary to public order ("ordre public") or morality shall not be a patentable invention; however, the working of an invention shall not be deemed to be so contrary merely because it is prohibited by any law in force in Hong Kong."*

"Morality" or "social ethics" does not have a strict definition and, in fact, may even change with time when more understanding is gained for a particular issue. Currently, Europe (EP) and China has a slightly different interpretation of "morality" on hESC-related technologies. In EP, EPC Rule 28 explicitly states that it is human embryos instead of hESC that are excluded for moral reason:

> *"Under Article 53(a), European patents shall not be granted in respect of biotechnological inventions which, in particular, concern the following:……(c) uses of human embryos for industrial or commercial purposes;……"*

Inventions involving hESC are patentable as long as a method for preparing the hESC which does not involve the destruction of human embryos[11]. On the other hand, China is much more stringent on inventions involving hESC. Guidelines for Patent Examination[12] explicitly states that:

> *"Both an embryonic stem cell of human beings and a preparing method thereof shall not be granted the patent right in accordance with the provisions of Article 5.1"*

In a 2012 decision[13], the patent reexamination board also indicated that a patent will only be granted if the hESC involved in an invention are obtained from well-established cell lines.

While the HKIPD did not issue any guidelines on interpreting the "morality" term with respect to hESC, a simple search on the HKIPD system shows at least 5 patent application titles containing the term "human embryonic stem cell"[14]. The Council on Human Reproductive Technology, which is the licensing authority for reproductive technology services and embryo research, published the "Code of Practice on Reproductive Technology and Embryo Research" in January 2013 and listed principles to be observed when patenting hESC in Appendix VII of this code[15]. In brief, like its EP counterpart, the focus is on forbidding uses of human embryos for industrial or commercial purposes and embryonic stem cell lines with identified functions may be patentable. Statistics from the Hong Kong tourism board shows that Hong Kong has over 3 million visitors from Mainland China every month[16] (FIGURE 2) and it could be foreseen that, with the completion of the high-speed rail link and bridge to Macau and Zhuhai, the influx of Mainland visitors would further increase and potentially open up market for healthcare products/services in Hong Kong[17]. This difference in patentable subject matter in Hong Kong may open up doors for foreign hESC-based products/services to the Chinese market which would otherwise be unprotected if they enter the Chinese market directly.

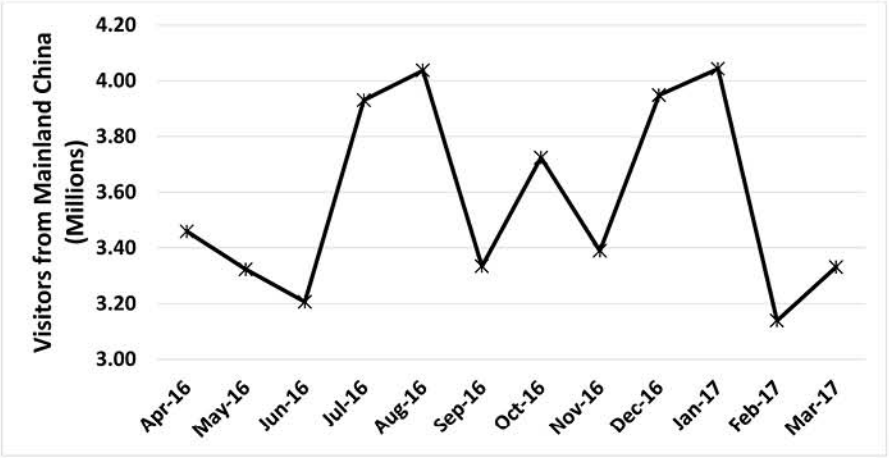

FIGURE 2. Visitor arrival statistics 2016-2017

SHORT TERM PATENT

The Hong Kong patent system also has its own merits for protecting innovation. The short-term patent is an under-utilized yet powerful tool in the Hong Kong patent system. The application process for the Hong Kong short-term patent is shown in FIGURE 1B. In most jurisdictions, a patent application is published before undergoing substantive examination. During substantive examination, an examiner will evaluate the patentability of an invention by comparing it with the prior art obtained in a search. The two most important patentability requirements which must be met would be novelty and inventive step of the invention. In brief, novelty refers to whether there is any difference between an invention and the prior art, while inventive step refers to whether a skilled person can arrive at this difference, if any, based on a combination of prior arts or existing knowledge.

Many countries have an "absolute novelty" requirement whereby a disclosure anywhere in the world represents valid prior art against a patent application. Therefore, once a patent application is published, its specification will serve as prior art for all patent applications filed after its publication date, including those filed by the same inventor. Most of the time an inventor will conduct a prior art search before filing an application, but no one can be sure if an examiner will obtain references outside the results of the inventor's prior art search with their professional skills. If a certain invention in a first application does not meet the patentability requirement during substantive examination, a subsequent application of a modified invention aimed at overcoming the rejections cited against the first application will need to clear a much higher hurdle. This is because, as mentioned above, the first application is now a prior art against the second application and the difference between the first and second applications (instead of references cited in the first examination) must be sufficiently large to overcome any rejections for lack of inventive step.

The Hong Kong short-term patent provides an alternative route to this issue because it will not be published unless a search report is furnished to the HKIPD and the short-term patent is granted[18]. As mentioned previously, one of the three designated patent offices or ISA will examine an invention for its patentability in this search report. If an adverse report is received and the applicants do not see any prospect for overcoming the rejections, one can choose not to submit the search report and lead to abandonment of the short-term patent without publication so that modification of the invention can still be made without affecting the absolute novelty of this invention. On the other hand, if the search report is positive and the applicant is confident of the search results, one can proceed to file foreign applications claiming priority to this Hong Kong short-term application. With Hong Kong being a WTO member and also covered by the Paris Convention and PCT[19], the Hong Kong short-term patent can be the first filed application to serve as priority basis to enter more than a hundred jurisdictions. An illustrative example is shown in FIGURE 3.

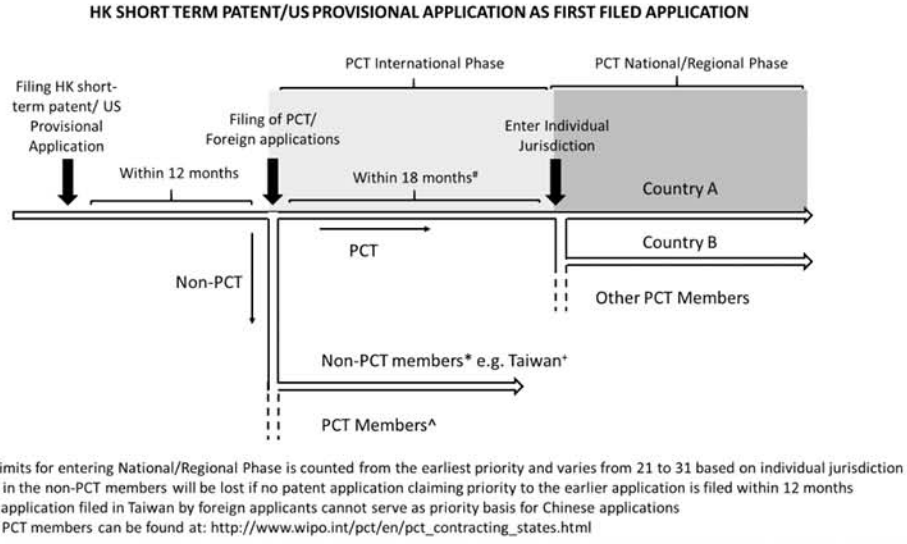

FIGURE 3. Using HK Short-term Patent/ US Provisional Application as First Filed Application

Since the Hong Kong patent system is designed to allow for applications in both English and Chinese languages[20], an applicant can draft and submit in his preferred language and obtain an early priority date without the need for translation which would be required if, for example, submitting to China directly when the draft is prepared in English. China's State Intellectual Property Office (SIPO)'s search report is usually ready within 15 to 30 days so that one could determine the patentability of an invention within a relatively short timeframe.

FOREIGN LICENSE REQUIREMENT

In most jurisdictions, an invention described in a patent application must seek approval from the government before the invention could be exported. This approval is usually in the form of a foreign filing license. The main purpose of this is to protect national security and inventions which are denied a foreign license are usually sensitive technologies that the government renders as potentially detrimental to the safety of the country if exported. Common technologies in this category include nuclear technology, atomic energy materials and biological warfare materials, etc.

In the United States (US), 35 U.S.C. Section 184 provides that:

> *"Except when authorized by a license obtained from the Commissioner of Patents a person shall not file or cause or authorize to be filed in any foreign country prior to six months after filing in the United States an application* for patent or for the registration of a utility model, industrial design, or model in respect of an invention made in this country."*

For every US-origin patent application filed with the United States Patent and Trademark Office (USPTO), an implicit petition is considered to be filed for a foreign filing license. Therefore, inventions made in the US will be automatically scrutinized for the need of a foreign license as long as a patent application is first made in the USPTO. The filing receipt of the application, which is usually issued within 2-3 weeks after the filing date, will indicate if the foreign filing license is granted. The foreign filing license is effective on the date shown on the filing receipt.

China used to have a similar foreign license requirement when inventions made in China are involved, whereby the invention will meet the foreign filing requirement as long as a first application was filed with SIPO.

Article 20 paragraph 1 (2001):

> *"Where any Chinese entity or individual intends to file an application in a foreign country for a patent for invention-creation made in China, it or he shall file first an application for patent with the patent administration department under the State Council, appoint a patent agency designated by the said department to act as its or his agent, and comply with the provisions of Article 4 of this Law."*

However, the amendment made in 2008 has complicated the situation such that an implicit request for confidentiality examination is included only for PCT applications. A separate confidentiality examination has to be requested even if a foreign application is claiming priority to a first Chinese patent application via a non-PCT route.

Article 20 paragraph 1 (2008):

> *"Any unit or individual that intends to apply for patent in a foreign country for an invention or utility model accomplished in China shall submit the matter to the patent administration department under the State Council for confidentiality examination. Such examination shall be conducted in conformity with the procedures, time limit, etc. prescribed by the State Council."*

If a foreign filing license is not requested before a foreign patent application is filed, the same invention will not be granted patent rights in China. If the patent application is related to security or other vital state interests, then criminal penalties will result for the applicant. The processes for requesting this confidentiality examination is shown in FIGURE 4. The time required could be as short as two to six weeks but could be as long as 10 months before approval from SIPO is granted.

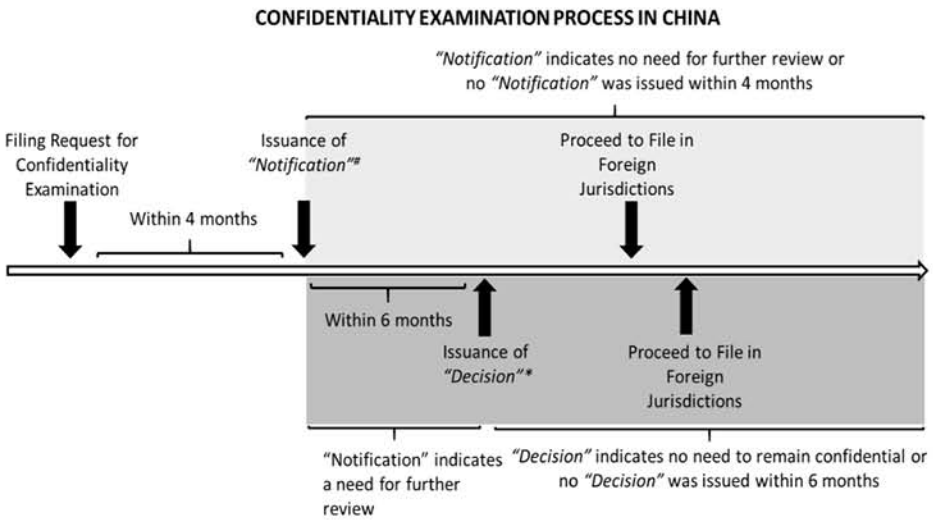

FIGURE 4. Confidentiality Examination Process in China

In comparison to China and the US, Hong Kong has no restrictions on foreign filing and any invention can be directly filed in any jurisdictions. This opens up opportunities for any invention developed in Hong Kong to tap into the advantages of foreign patent systems. For example, the US provisional application is sometimes a useful tool for preserving a priority date because of the reduced paperwork and filing requirements, as compared to most other types of patent applications.

The minimum requirements to secure a filing date with a US provisional application:

(1) a cover sheet indicating the names and residence of the inventor, title of the invention, etc.;

and

(2) an enabling specification describing the invention.

Claims and drawings for the understanding of the invention are optional. Even filing fees can be paid at a later time with surcharge payment. Formalities such as the oath or declaration from the inventor(s) and information disclosure statements for disclosing prior art references are not required in provisional applications. As such, it is less time-consuming and less costly to put together a US provisional application as compared to most other types of patent. In situations where unavoidable disclosure of an invention is expected, e.g. meeting a potential licensee, the provisional application offers a last minute solution to protect one's IP rights. While non-disclosure agreements (NDA) may also be used to contractually prevent the other party from disclosing or using the technology, whether the other party can be trusted to honor the NDA would be another issue. Once confidential information is disclosed, any third party will be able to use that information without any duty to honor the NDA. Filing a provisional application may be a better alternative by placing on official record the technology in the possession of a company on a specific date. By filing a lower-cost U.S. provisional application at the earliest possible date, the inventor can also begin promoting the invention, seeking licensees and partners, and raising money to develop and commercially exploit the technology. Despite being "provisional", non-provisional or foreign patent applications claiming priority to this application can be filed within the next 12 months to obtain patent rights on the invention (See FIGURE 3).

The US provisional application is just an example on how Hong Kong's flexible patent law allows locally developed technologies to use foreign tools for IP protection. Further exploration of the different patent systems around the world may result in many other tools which local companies can utilize.

LOCAL RESOURCES

The Innovation and Technology Commission (ITC) provides several programs under the Innovation and Technology Fund (ITF) to encourage the private sector to invest in research and development activities. The number of projects and amount funded in each technology area are shown in FIGURE 5A and B [21].

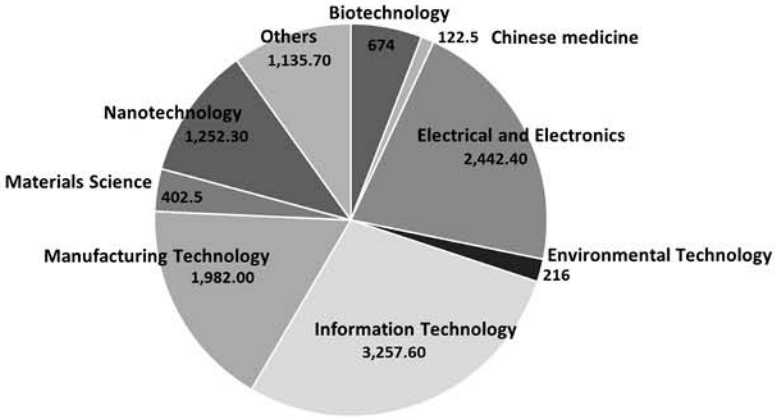

FIGURE 5A. ITF funding (Millions) in each technology area

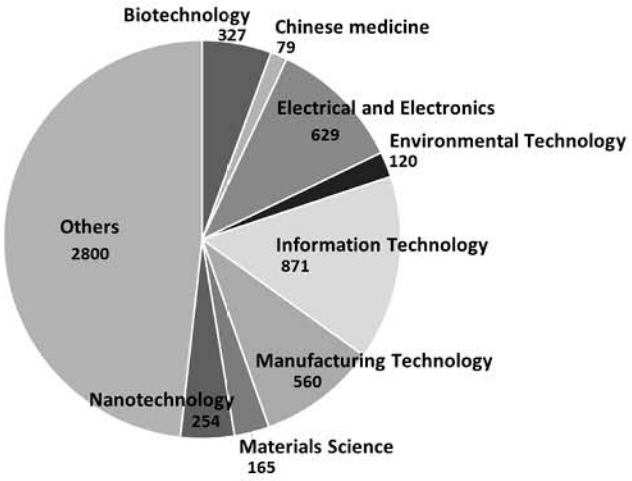

FIGURE 5B. ITF funded projects in each technology area

Although many of the programs are only available to HK universities/research institutions and their collaborators, there are funding initiatives such as Enterprise Support Scheme (ESS) for private companies and startups to fund their R&D activities[22]. Funding support of up to HK$10 million may be provided on a dollar-for-dollar matching basis. The applicant will also be able to retain full ownership of all intellectual property rights arising from the funded project and no recoupment of Government's contribution is required. Benefit-sharing of commercialized R&D results arising from the funded project is also not mandatory.

Hong Kong companies and individuals are also eligible for the Patent Application Grant (PAG) which is another funding scheme administered by the ITF to apply for patents to protect their own innovations. PAG is currently capped at HK$250,000 and ownership of the granted patent will remain with the applicant.

CONCLUSION

From the patent law perspective, Hong Kong's patent system that accommodates features from both European and Chinese patent law may make it attractive for certain high-tech industries. For example, the difference in patentable subject matter between Hong Kong and China may open up opportunities for products/services that is non-patentable in China. Its unique short-term patent, which substantively examines an invention before publication, provides a route for determining patentability by an authority before disclosure. This allows the possibility for further modifications to an invention to be made and a second application to be filed when the invention does not meet the patentability requirements. Hong Kong also does not have any foreign license requirement so that inventions developed in Hong Kong can readily tapinto advantages of the patent system in any foreign jurisdictions. In summary, Hong Kong has excellent hardware for innovative activities but this potential must be unleashed before it could transform to the innovation and technology hub envisioned by its government.

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Chapter 15

SACRIFICING THE PATENTABILITY STANDARD OF NOVELTY AND INDUSTRIAL APPLICATION ON THE ALTAR OF INCREMENTAL BIOTECH INNOVATION IN HONG KONG

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ABSTRACT

Despite non-novelty and the non-susceptibility of industrial application for a diagnostic, therapeutic or surgical treatment, most jurisdictions, including Hong Kong, have chosen to allow first and further medical use claims. Hong Kong's new patent system includes, for the first time in its history, the possibility of applying for an Original Grant Patent. It is expected that the Patent (Amendment) Bill 2015 will come into effect in 2018. This article first focuses on the patentability requirements for medical use claims, their failure and solution. Like an alchemist who is forging gold out of lead, the new Hong Kong patent ordinance purifies the failures of these patentability requirements by using two fictions (Sections 9(B)(5) and 93(4) Patents Ordinance). After this doctrinal hurdle is overcome, the Hong Kong patent system pragmatically allows for straightforward purpose-limited claims, but also for Swiss-type claims. Even though Hong Kong followed the UK and EPO in accepting the Swiss-type claim, it does not follow them in their subsequent rejection of this convoluted claim, because Hong Kong's patent system wants to continue to be able to re-register Chinese innovation patents that are phrased as Swiss-type claims.

The advantages and disadvantages of first and further medical use, methods of delivery and patient groups are explored. In case of a slew of ever more obscure uses, it seems, at least prima facie, the scales are tipped towards protection of extending originators' patent rights which is not conducive for generics and the access to reasonably priced medicines, but might be positive for efficacy studies.

The article will pose the age old question as well: will a patent-friendly but potentially access-unfriendly approach harness or harm innovation in biotech? Here a distinction will be made between the different kinds of innovation, such as claims for polymorphs, enantiomers (optical isomers), salts, ethers, esters, compositions, doses, prodrugs, metabolites, analogy processes, and Markush and selection claims. The article will explore the possibility of reconciling the granting of patents for second and further medical use claims, with an enhanced efficacy and utility regime conforming to the respective Canadian and Indian legal innovations. At least this way, these medical uses will demonstrate incremental but observable improvements for patients.

Sacrificing the Patentability Standard of Novelty and Industrial Application on the Altar of Incremental Biotech Innovation in Hong Kong

Dr. Danny Friedmann*

Section 1. Introduction

> "And while he dreams of finding in the fire
> that true gold that will put an end to dying,
> God, who knows His alchemy, transforms him
> to no one, dust, oblivion."[1]

The rationale behind the grant of an invention patent, an exclusionary right limited in scope, duration and effect,[2] provides on the one hand an incentive to innovate for individuals, and on the other hand procures information for the rest of the industry, which must help elevate the level of innovation in society.[3] Or to put it eloquently as Peter Rosenberg: "the inventor makes a truly Faustian bargain",[4] by removing the necessity of obfuscating the invention,[5] disclosing the invention[6] in a formalised way so that a person skilled in the art will know how to practise it,[7] in return for a

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1 Jorge Luis Borges, SELECTED POEMS, VOLUME 2, The Alchemist (Penguin Books: London, 2000) 223, last paragraph.

2 The question with, for example, genetic diagnostics methods is whether a second opinion, where another laboratory needs to resequence the patient's genes, exhausts the patent or not. See Kevin Noonan, The Relevance of Patent Exhaustion in the Myriad Genetics Case, PatentDocs, 14 December 2010, available at: http://www.patentdocs.org/2010/12/the-relevance-of-patent-exhaustion-in-the-myriad-genetics-case.html. Arti K. Rai, Diagnostic Patents at the Supreme Court, 2013 Annual Helen Wilson Nies Lecture, 18 MARQ. INTELL. PROP. L. REV. 1, available at: https://pdfs.semanticscholar.org/1108/2cf9f6786457e5e1b068ced-18499ba613f0e.pdf. Paul Veravanich and John Kappos, Is The Supreme Court Exhausted With Patents? Orange County Business Journal, 2 September 2008, available at: https://www.omm.com/files/upload/IsTheSupremeCourtExhaustedWithPatents.pdf.

3 William Cornish, David Llewelyn and Tanya Aplin, INTELLECTUAL PROPERTY: PATENTS, COPYRIGHT, TRADE MARKS AND ALLIED RIGHTS (8th edition, Sweet & Maxwell: London, 2013) 143.

patent.[8] Does society make an even more Faustian pact in the case of biomedical pharmaceuticals? In its quest for knowledge to raise the state of the art, does it sell its soul by granting patents to exclude others from accessing, for two decades, the patented medical inventions and protecting a premium price for patented medicines?[9] However, one can also argue that the patent system helps inventors as a Smithian hand to coordinate their efforts and explore alternative solutions by working around existing patents.[10] In principle, after the patent has expired, pharmaceutical companies can start manufacturing and selling these generic versions of the medicine. However, this turns out to be often more challenging in practice.[11]

Since Hong Kong is a Special Administrative Region of the People's Republic of China, its governance falls under its constitution, which is called the Basic Law. Similar to the Intellectual Property Clause of the U.S. Constitution,[12] the Hong Kong government should, on its own, formulate policies on science and technology. Also, it should protect by law the achievements in scientific and technological research, patents, discoveries and inventions.[13] Instead of exclusively re-registering patents from the designated patent offices of China, EPO or the UK, the Patent (Amendment) Bill 2015, which was accepted in 2016 and will go into effect in 2018, will introduce also the possibility of granting an Original Grant Patent. China's State Intellectual Property Office is helping Hong Kong with the acquisition of the knowledge and skills of how to do substantial examinations.[14] Just as most jurisdictions, Section 93 Patent Ordinance 1997 prescribes the following validity standards for patents; novelty,[15] inventive step,[16] enablement and industrial application. All crucial components in raising the state of the art.

4 "The purpose of disclosure to the public is to catalyze other inventors into activity. ... The inventor makes a truly Faustian bargain with the sovereign, exchanging secrecy of indefinite and of possibly perpetual duration, for ephemeral patent rights." Peter Rosenberg, PATENT LAW FUNDAMENTALS, Clark Boardman Co. 1975, 7.

5 One could also consider alternative ways to incentivize inventors to invent; including direct grants, patent pools and public databases. See Scott Woolley, 'Prizes Not Patents' Forbes, 19 April 2006, available at: https://www.forbes.com/2006/04/15/drug-patents-prizes_cx_sw_06slate_0418drugpatents.html.

6 Devlin argues that in case of conflicts between the incentivize-to-invent doctrine and the disclosure doctrine, the first should prevail, since the latter is merely ancillary to the first. Alan Devlin, The Misunderstood Function of Disclosure in Patent Law (2010) 23(2) HARVARD JOURNAL OF LAW AND TECHNOLOGY 401.

7 Sven Bostyn, Enabling Biotechnological Inventions in Europe and the United States. A study of the patentability of proteins and DNA sequences with special emphasis on the disclosure requirement, Eposcript Series, no. 4, EPO, München, 2001, passim.

8 Although there is an additional quid pro quo incentive: market exclusivity; research in return for the right to commercialize the invention, even if the patent has expired, this falls beyond the scope of this article.

9 In Myriad Genetics opponents of patenting isolated natural occurring DNA sequences (such as BRCA1 and BRCA2 that can help detect high risk of breast and ovarian cancer) argued that cancer research would be stifled and limit options for cancer patients in seeking genetic testing. The Supreme Court held that the diagnostic claims were not patent eligible, because they claim genetic information that is produced by nature. In Association for Molecular Pathology, et al. v Myriad Genetics, Inc., et al. 133 S.Ct. 2107, 13 June 2013.

10 Bostyn and Petit distinguish two forms of 'competition by substitution'; the competition by 'follow on innovators' and that by 'pioneer innovators'. Sven Bostyn and Nicolas Petit, Patent=Monopoly: A Legal Fiction (December 31, 2013), available at: https://ssrn.com/abstract=2373471, 7.

11 Carrier has written about the diverse ways generics are blocked from the market. For example via reverse patent settlements and denying them samples. See the respective articles: Michael Carrier, Unsettling Drug Patent Settlements: A Framework for Presumptive Illegality (2009) 108 MICHIGAN LAW REVIEW 27; Michael Carrier, A Simple Way to Lower Drug Prices, IP Watchdog, 24 June 2016, available at: http://www.ipwatchdog.com/2016/06/24/simple-way-lower-drug-prices/id=70314/.

12 Article I, Section 8, Clause 8, of the U.S. Constitution grants Congress the power "[t]o promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries".

13 Article 139 Basic Law of Hong Kong S.A.R. of China 1997: "The Government of the Hong Kong Special Administrative Region shall, on its own, formulate policies on science and technology and protect by law achievements in scientific and technological research, patents, discoveries and inventions."

14 Danny Friedmann, EDITORIAL: First thoughts on Hong Kong's new patent system; second thoughts on its further medical use claims, 11(12) JOURNAL OF INTELLECTUAL PROPERTY LAW AND PRACTICE (Oxford University Press, 2016) 871-872, https://academic.oup.com/jiplp/article/11/12/871/2335244/First-thoughts-on-Hong-Kong-s-new-patent-system?key-type=ref&ijkey=hxzrNyz5HJb8Omj.

15 Although patent rights are territorial, the requirement of novelty of Section 94(2) Patent Ordinance 1997 is tested in relation to the state of the art that comprises everything available to the public in Hong Kong or elsewhere, or anticipated by a person skilled in the art. If an invention has already been claimed in a patent, another patents does not deserve to be registered covering the same claims. In that case, the prior patent holders can make use of the right of priority, according to Article 4(C) Paris Convention for the Protection of Industrial Property and Articles 2 and 29 Agreement on Trade-Related Aspects of Intellectual Property Rights, which can expand their realm of protection within a 12 months after the date of filing the application. Conform Article 153 Basic Law, the Paris Convention also applies to Hong Kong with effect from 1 July 1997 via China's membership, see Paris Notification No. 178 of 6 June 1997. Conform Article 151 Basic Law, Hong Kong is an independent member of WTO since 1 January 1995, and thus member of the Agreement on Trade-Related Aspects of Intellectual Property Rights, which is an integral part of the Agreement on the World Trade Agreement.

16 Section 96(1) Patent Ordinance 1997: "An invention shall be considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art."

Section 2. Methods of medical treatment not susceptible for industrial application

Article 27(3) of the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) allows World Trade Organization members to exclude "diagnostic, therapeutic and surgical methods for the treatment of humans or animals" from patentability. The reason for this possibility is that jurisdictions should be able to immunize their health professionals, such as doctors, hospitals, and indirectly their pharmacists, from the liability of patent infringement.[17] However, many jurisdictions including Hong Kong have decided to tolerate the protection of methods of medical treatment via patents under certain circumstances.

Article 93(4) of the Hong Kong Patent Ordinance 1997 states that a method for treatment of the human or animal body by surgery or therapy and a diagnostic method practised on the human or animal body shall not be regarded as an invention which is susceptible of industrial application for the purposes of novelty and inventive step.[18] However, the second sentence of Article 93(4) states that deficiencies that would lead to non-susceptibility of industrial application do not apply to a product, and in particular a substance or composition, for use in any such method. Section 9(B)(5) of the Patents (Amendment) Bill 2015 makes clear that first and further medical use of the product/substance or composition will be regarded as new. This legal fiction enables a slew of medical patent claims that, at first sight, seem to protect marginal improvements. Practically, these claims can be drafted via directly phrased purpose-limited product claims[19] or the convoluted Swiss-type claims. Since Abbott GmbH v Pharmareg Consulting Company Ltd in 2009,[20] Hong Kong followed the UK and the EPO in allowing Swiss-type claims.[21] But when the UK and EPO rejected Swiss-type claims in 2010,[22] Hong Kong continued to allow these drafts for the re-registration of Chinese patents that were expressed in this sort of claim. Under the amended patent law, it will allow claims to be drafted in both forms.

17 In the US there is no statutory prohibition against patenting methods of medical treatment. Instead Congress amended the Patent Act in 1996: 35 USC § 287(c), which exempts licensed medical professionals (e.g. doctors) and related health care entities (e.g. hospitals) from liability for infringement of medical method patents.

18 In Myriad Genetics the Supreme Court makes clear that therapeutic method patents are allowed under US patent law. "It is important to note what is not implicated by this decision. First, there are no method claims before this Court. Had Myriad Genetics created an innovative method of manipulating genes while searching for the BRCA1 and BRCA2 genes, it could possibly have sought a method patent. ...." Supra note 9. Holbrook concludes that there is differential treatment for method patents. Timothy Holbrook, Method Patent Exceptionalism

To avoid that pharmaceutical companies could register patents for known compounds for new uses to substitute their expired patents (a manoeuvre referred to as "evergreening"), India amended its law in 2005 by setting an enhanced efficacy standard for these kinds of inventions:

> Article 3 Patent (Amendment) Acts 2005: "The following are not inventions within the meaning of this Act, (...)
> (d) the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant."[23]

It is India's policy to incentivize the development of medicines that increase efficacy, prevent patent thickets and provide space for generic companies to manufacture inexpensive medicines. Considering the Indian policy, the next section will take the degree of efficacy enhancement into account when analysing new medical uses of known compounds.

19 Purpose-limited product claims are drafted in this way: "X for use in the treatment of Y." See definition and case law at 7.2.3 Purpose-limited product claims and Swiss-type claims – scope of protection, EPO, available at: http://www.epo.org/law-practice/legal-texts/html/caselaw/2016/e/clr_i_c_7_2_3.htm.

20 Abbott GmbH & Another v Pharmareg Consulting Company Ltd & Another [2009] 3 HKLRD 524 (HK Court of First Instance).

21 Swiss-type claims are drafted in this way: "Use of X for the manufacture of a medicament for the treatment of Y." Supra note 19.

22 G 0002/08 (Dosage regime/ABBOTT RESPIRATORY) 19 February 2010, ECLI:EP:BA:2010:G000208.20100219.

23 For a comprehensive legal and historical analysis of Section 3(d) Patents (Amendment) Act 2005, see Feroz Ali, THE ACCESS REGIME: PATENT LAW REFORMS FOR AFFORDABLE MEDICINES (Oxford University Press, 2016).

Section 3. Bioequivalent or not bioequivalent, that's the question

Each jurisdiction has to make policy decisions about what kind of patent claims of known compounds used in a new way are acceptable, to what degree and under which conditions? In the case of Hong Kong, this Special Administrative Region wants to be on the one hand a respected member of the international community, and protect the very high investments into research and development by the biotech and pharmaceutical industry, especially since the costs of copying in these industries are particularly low.[24] On the other hand, Hong Kong should also guarantee the access of its population to affordable medicines, which can be expedited by using high patentability standards. To balance these interests, legislators, courts and examiners can mix these interests, using the novelty, inventiveness and industrial application requirements as control sliders.[25]

As time goes by, most chemical compounds are already part of the prior art. For pharmaceutical companies it becomes ever harder to come up with new compounds. Therefore, pharmaceutical companies who stand on the edge of the patent cliff,[26] when their products are about to go off-patent, are looking for ways to patent near bioequivalents.[27] Patenting these new uses and forms of known compounds can help them to get a follow-on patent, which can function as a parachute, helping them to delay and soften the landing from the patent cliff.

24 This "sweat of the brow" justification –- diligence is sufficient, no need for substantial creativity -, originates from Locke. John Locke, TWO TREATISES OF GOVERNMENT, Second Treatise of Government, (P. Laslett rev. ed. 1963 3d ed., 1698) 138-140. See Justin Hughes, The Philosophy of Intellectual Property (1988) 77 GEO. L.J. 287.

25 Sometimes patent ineligibility is also used in the mix. In Mayo v Prometheus, the Supreme Court held a correlation between naturally-produced metabolites and therapeutic efficacy and toxicity to be an unpatentable "natural law". Instead of determining patent ineligibility, the court could have come to the same outcome by determining a lack of inventive step. Mayo Collaborative Services, DBA Mayo Medical Laboratories, et al. v. Prometheus Laboratories, Inc. 132 S. Ct. 1289 (2012). Judge Rader argued that the language used in Mayo Such "should not be read to conflate principles of patent eligibility with those of validity, however. Nor should it be read to instill an "inventiveness" or "ingenuity" component into the inquiry. In CLS Bank Int'l. v Alice Corp. Pty. Ltd., 717 F.3d 1269 (Fed. Cir. 2013) 99.

26 The patent cliff is an informal description of the situation where a brand pharmaceutical is about to go off-patent, which will cause its revenues to nose-dive, since it will be legitimately replicated and sold by generics, at lower prices.

27 "T]he absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study." Code of Federal Regulations, Title 12, United States Food and Drug Administration.

28 Carlos Correa, Guidelines for Pharmaceutical Patent Examination: Examining Pharmaceutical Patents from a Public Health Perspective, United Nations Development Programme (2015).

The challenge for pharmaceutical companies is to convince the patent office of the difference and surprising enhanced efficacy of the new form in comparison to the old form of the known substance. The challenge for patent offices, which are representing the public interest, is to guarantee that pharmaceutical companies are incentivized to invent new medicines, but also to make sure that the public has access to affordable medicines.

An explanation of Section 3(d) Patents Act of India enumerates a list of substances that have similar properties with regard to efficacy:

> "salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy".

Two guidelines for pharmaceutical patent examination, both authored by Carlos Correa in 2015[28] and 2006,[29] discuss the absence of the desirability to patent the following forms of known substances: claims for polymorphs,[30] enantiomers (optical isomers),[31] salts,[32] ethers,[33] esters[34], compositions,[35] doses,[36] prodrugs,[37] metabolites,[38] analogy processes,[39] and Markush[40] and selection claims.[41] To illustrate the controversy over the patentability of these (near) bioequivalent forms, three varieties will now be explored below: polymorphs, enantiomers and salts. The recurring theme will be whether the form is new or inventive and has industrial applicability. One can often observe paradoxes in intellectual property law.[42] Also patent law is not immune from paradoxical questions. Does a new form of a known substance lead to the same or a different substance? Applying Mulisch' octavism doctrine to this paradox can offer some guidance: a new form of a known substance is like the music note C (for example the one with a frequency around 131 Herz) that is and is not the same C an octave higher (this is the middle C at a frequency of 262 Herz) to our ears.[43]

Polymorphs

Polymorphism is the ability of a chemical molecule or ions to exist within different internal crystal structures. Correa argues that this is an inherent property of a substance, and therefore they are not created but discovered.[44] According to Correa, patents for polymorphs should be denied on the ground of absence of a patentable invention or inventive activity.[45] Correa wrote that obtaining a polymorph is a routine activity in pharmaceutical production, carried out through methods widely known to

a person skilled in the art. Only a process used for the preparation of a polymorph, if novel and involving inventive step, may be patentable. The 2006 Working Draft acknowledged that different polymorphs of a drug can have substantially different functional characteristics, and that changing the polymorphic form of a drug active ingredient can result in effects such as altered bioavailability, or a change in the long-term stability profile.[46] Nevertheless Correa still argued that polymorphs are part of the prior art.[47] In contrast to this, Holman points to Glaxo Group Ltd. v Apotex, Inc.,[48] where the US Court of Appeals for the Federal Circuit held that the patent on the polymorph of the cefuroxime axetil[49] was valid.[50] A generic company had challenged the patent validity for obviousness since a previous patent of Glaxo[51] had disclosed the same active ingredient cefuroxime axetil in the forms of (1) an impure amorphous[52] compound and (2) a purer crystalline[53] compound. However, according to the Federal Circuit, the previous patent did not suggest that "highly pure amorphous cefuroxime axetil product would have better bioavailability and stability than a crystalline form".[54] Therefore it rejected the claim of non-obviousness.

29 Carlos Correa, Guidelines for the Examination of Pharmaceutical Patents: Developing a Public Health Perspective – Working Paper, ICTSD, UNCTAD and WHO (2006).
30 Supra Section 3.
31 Ibid.
32 Ibid.
33 John Waite, The Patentability of a Principle of Nature (1917) 15(3) MICH. L. REV. 243.
34 See for example Dome Patent L.P. v Michelle K. Lee, Director, USPTO, [Opinion] 14-1673 (Fed. Cir. 2014) 3 September 2015, available at: http://www.cafc.uscourts.gov/sites/default/files/opinions-orders/14-1673.Opinion.9-1-2015.1.PDF.
35 See for example Thorsten Bausch, Medeva and the Limitation of Composition Claims, Kluwer Patent Blog, 10 October 2013, available at: http://kluwerpatentblog.com/2013/10/10/medeva-and-the-limitation-of-composition-claims/.
36 Infra Section 4.
37 See for example Amy Kapczynski , Chan Park , Bhaven Sampat, Polymorphs and Prodrugs and Salts (Oh My!): An Empirical Analysis of "Secondary" Pharmaceutical Patents, PLOS One, 5 December 2012, available at: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0049470.
38 See for example Richard Li-dar Wang, Pei-Chen Huang, Patent Protection of Pharmacologically Active Metabolites: Theoretical and Technological Analysis on the Jurisprudence of Four Regions (2012) 29 SANTA CLARA HIGH TECH. L.J. 489.
39 "It is well established that analogy processes are patentable insofar as they provide a novel and inventive product. This is because all the features of the analogy process can only be derived from an effect which is as yet unknown and unsuspected (problem invention)." T 0119/82 (Gelation), EPO, 12 December 1983, ECLI:EP:BA:1983:T011982.19831212.
40 See for example Richard Bone, The Death of the Markush Group, 247th American Chemical Society National Meeting Dallas TX, 20 March 2014, available at: http://www.vlplawgroup.com/pdf/ACS_Dallas2014_RichardBone.pdf. Kimberly Prior, The USPTO's Historic Struggle with Markush Claims: Will the 2011 Guidelines Provide Relief? (2012), Law School Student Scholarship, Paper 114, available at: http://scholarship.shu.edu/student_scholarship/114.

Enantiomers

Enantiomers (optical isomers) are a pair of molecules that are mirror images of each other. They share the same chemical formula. The difference resides in the three-dimensional arrangement of molecular constituents around a single carbon atom in the compounds: classified as either right- or left-handed. Chirality, when the molecule is non-superimposable on its mirror image, is relevant for most biomolecules and pharmaceuticals. Correa argued that isolated enantiomers should not be deemed patentable when the racemic mixture, which has an equal amount of left- and right-handed enantiomers of a chiral molecule, was previously disclosed.[55] According to Correa, processes for the separation and purification of enantiomers may only be patented if novel and inventive.[56] However, as Holman demonstrated, in Forest Laboratories, Inc. v Ivax Pharmaceuticals, Inc.,[57] the Federal Circuit held that prior art disclosing a racemic mixture did not render a purified enantiomer obvious. Instead, the court found that attempting to separate the enantiomers of citalopram based on the knowledge of one of ordinary skill in the art would have required undue experimentation. The court held that the Smith reference, despite of referring to the

41 "Novelty by selection cannot be claimed, since none of the possible combinations of all the listed starting compounds and process variants introduce a new element - indispensable for substance selection - that would result in a true and not just "identical" modification of the starting substances." T 0012/81 (Diastereomers) EPO, 9 February 1982, ECLI:EP:BA:1982:T001281.19820209.
42 Respectively about the paradoxes found in trademark law, geographical indications law and copyright and design rights law: Neil Wilkof, Paradoxes and intellectual property law (2013) 8(6) JOURNAL OF INTELLECTUAL PROPERTY & PRACTICE 423 and Michelle Agdomar, Removing the Greek from Feta and Adding Korbel to Champagne: The Paradox of Geographical Indications in International Law" (2008) 18 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 541, and Kal Raustiala and Christopher Sprigman, The Piracy Paradox: Innovation and Intellectual Property in Fashion Design (2006) 92 VIRGINIA LAW REVIEW 1687.
43 Mulisch (1927-2010) in Dutch: "De tweede toon is niet identiek met de eerste, maar ook niet niet identiek." (The second tone is not identical to the first, but also not not (sic) identical.) Harry Mulisch, DE COMPOSITIE VAN DE WERELD (Bezige Bij, Amsterdam: 1980), 113, passim.
44 Correa 2015, supra note 28, 9.
45 Ibid.
46 Correa 2006, supra note 29, 10.
47 Ibid.
48 Glaxo Group Ltd. v Apotex, Inc., 376 F.3d 1339, 1342-43 (Fed. Cir. 2004)
49 U.S. Patent Number 4,562,181.
50 Christopher Holman, In Defense of Secondary Pharmaceutical Patents: A Response to the UN's Guidelines for Pharmaceutical Patent Examination, (September 2, 2016), Indiana Law Review, Forthcoming, available at: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2833983.

racemic mixture which included a purified enantiomer, as claimed by Ivax, was not enabled and was therefore not part of the prior art. Ivax also failed to prove that the patent was obvious. Instead, the court held that the person skilled in the art at the time of the invention would generally have been motivated to develop new compounds rather than undertake the difficult and unpredictable task of resolving a known racemate.[58]

Salts

About half the molecules used in medicinal therapy are administered as salts.[59] Bansal, Kumar and Amin explain that salification of a drug substance can overcome the suboptimal biopharmaceutical or physicochemical properties by pairing it to a counterion.[60] According to Correa, the preparation of salts with advantageous properties over the drug in its free base/acid form is part of the common knowledge of a person skilled in the art[61] and are therefore deemed obvious. In contrast to Correa, Holman pointed to Pfizer v Apotex in 2007,[62] where Federal Circuit Judge Newman in her dissent to the majority decision observed that "[b]oth sides acknowledge that the effects of chemical changes on properties of medicinal products is [sic] not predictable".[63]

51 U.S. Patent Number 4,267,320.
52 Amorphous = randomly distributed.
53 Crystallize = regularly recurring pattern.
54 Glaxo Group Ltd., supra note 48, D2 para 3.
55 Correa 2015, supra note 28, 10.
56 Ibid.
57 Forest Laboratories, Inc. v Ivax Pharmaceuticals, Inc., 501 F.3d 1263 (Fed. Cir. 2007).
58 Ibid.
59 And just as with other patent claims, novelty, non-obviousness and industrial application are requirements. In Pfizer Inc. v Apotex, Inc., the CAFC held that the claims 1-3 for the US Patent No. 4,879,303, entitled "Pharmaceutically Acceptable Salts" were obvious. Pfizer Inc. v Apotex, Inc. 480 F.3d 1348 (Fed. Cir. 2006) paragraph 80.
60 Arvind Bansal, Lokesh Kumar, Aeshna Amin, Salt Selection in Drug Development (2 March 2008) 32(3) PHARMACEUTICAL TECHNOLOGY, available at: http://www.pharmtech.com/salt-selection-drug-development.
61 Correa 2015, supra note 28, 9.
62 "[T]he prior art salts of amplodipine were plagued by a number of undesirable properties that stood in the way of creating an optimized product, such as stickiness, instability, low solubility and hygroscopicity, but these deficiencies were unexpectedly solved by development of the besylate salt of the drug." Holman, supra note 50, 21.
63 Pfizer, Inc. v Apotex, Inc., 488 F.3d 1377, 1379 (Fed. Cir. 2007)(Newman dissent). However, Bohrer argues in an email that given the very limited number of commonly used salts (around 20) the issue not the predictability is the likelihood of success in finding an acceptable salt, without "undue" experimentation.

Section 3(d) Patents Act of India, states that only new forms of known substances that enhance efficacy are patentable.[64] In Novartis AG v Union of India,[65] the Supreme Court of India held that the efficacy of beta crystalline form of Imatinib mesylate should be tested depending on the function, utility, or the purpose of the product under consideration. Thus for a medicine, the test should be therapeutic efficacy, which should be construed strictly and narrowly. The physico-chemical properties of beta crystalline form of Imatinib mesylate: better thermodynamic stability and lower hygroscopicity,[66] "may be otherwise beneficial but these properties cannot even be taken into account for the purpose of the test of Section 3(d), since these properties have nothing to do with therapeutic efficacy."[67] Increased bioavailability alone may not necessarily lead to an enhancement of therapeutic efficacy, as Ali points out: it should have been specifically claimed and established by research data.[68]

64 Ali, supra note 23, 96.
65 Novartis AG v Union of India AIR 2013 SC 1311, 2013 (54) PTC 1(SC), (2013) 6 SCC 1.
66 The hygroscopicity of a salt is that they readily dissolve in the water they absorb.
67 Novartis AG, supra note 65.
68 Ali, supra note 23, 100.

Section 4. The dose makes the medicine and stratified medicines

The alchemist Paracelsus is credited for the adage that "the dose makes the poison".[69] In the same vein, the right dose of a medicine has the most curative properties. Also, the right kind of patient will be optimally healed by a certain medicine. This raises questions whether a new dosage for a known substance, or a specific patient group for a known substance meets the standard of patentability. Does it lead to a difference in degree or in kind? Will a person skilled in the art anticipate the result or is it obvious?

Dosage

The U.S. Government Accountability Office criticized "[t]he practice commonly known as producing line extensions – deriving new products from existing compounds by making small changes to existing products, such as changing a drug's dosage".[70] Correa argued that claims over the dose of a drug fail to comply with the industrial applicability requirement.[71] Correa reasons that dosage claims should be qualified, in spite of their appearance, as a composition (or combination) claim. And since these combinations of known drugs are considered methods of treatment, they lack industrial applicability. Holman does not concur, since "a claim to a drug dose is no more equivalent to a method of using the drug than a claim to a novel active ingredient is equivalent to a claim to a method of using the active ingredient."[72] Holman pointed to Allergan, which had developed Lumigan, whose original formulation contained 0.03 percent of the active ingredient bimatoprost and 50 parts per million benzalkonium chloride.[73] The latter is a preservative that inhibits bacterial growth in ophthalmic solutions, but it can also damage the cells on the ocular surface. Allergan invested in research to reduce the negative side effects while maintaining therapeutic efficacy. This was achieved by reducing the dosage of the active ingredient in conjunction with an increased concentration of benzalkonium chloride. In Allergan, Inc. v Sandoz Inc.,[74] the Federal Circuit held that the claimed formulation by Allergan exhibited "unexpected results," which differed from the prior art. It meant "the difference between an effective and safe drug and one with significant side effects that caused many patients to discontinue treatment"[75].

Sanofi-Aventis Deutschland GmbH v Glenmark Pharmaceuticals Inc.,[76] makes clear that a reduction of dosages can lead to great improvements. Tarka is the patented combination antihypertension medicine that consists of the angiotensin converting enzyme inhibitor trandolapril and the calcium channel blocker verapamil hydrochloride and can be administered in a single dosage. Alternatives such as enalapril and captopril needed to be dosed, respectively two and three times per day.[77] These multiple dosages cause multiple imbalances in the human body and compliance problems.[78] In other words, dosages might lead not only to a difference in degree but also to a difference in kind in comparison to the prior art.

Stratified medicines

Because of genetic variations or other variations, people will respond differently to medicines[79] and/or how these medicines are administered. Towards the end of a patent life-cycle, pharmaceutical companies will be stimulated to classify patients into groups that are most susceptible for a pharmaceutical or medical intervention if certain biomarkers or combination of biomarkers are determined via diagnostic tests.[80] To patent the claims for known substances and new medical use or diagnostics for stratified medicine[81] objections of non-patentability and non-novelty need to be overcome.[82]

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69 The Latin adage Sola dosis facit venenum was credited to Theophrastus Philippus Aureolus Bombastus von Hohenheim, also known as Paracelsus (1493-1541).

70 Government Accountability Office, New Drug Development. Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts, Washington D.C, 2006, 34.

71 Correa 2015, supra note 28, 10.

72 Holman, supra note 50, 40.

73 Holman, supra note 50, 25, 26 and 40.

74 Allergan, Inc. v. Sandoz Inc., 796 F.3d 1293, 1306 (Fed. Cir. 2015).

75 Ibid.

76 Sanofi-Aventis Deutschland GmbH v Glenmark Pharm. Inc., USA, 748 F.3d 1354, 1356 (Fed. Cir.), cert. denied, 135 S. Ct. 759 (2014).

77 Response Brief of Plaintiffs-Appellees, Sanofi-Aventis Deutschland v Glenmark Pharmaceuticals, Inc., 2012 WL 5928463 at 12 (Fed. Cir.).

78 Non-compliance with drug therapy is a serious problem to society which can lead to superbugs resistant to antibiotics. See Antimicrobial resistance, factsheet, WHO, September 2016, available at: http://www.who.int/mediacentre/factsheets/fs194/en/.

79 Herceptin (trastuzumab) was not considered to be cost-effective by the Scottish Medicines Consortium and National Institute of Health and Clinical Excellence in the large gastric cancer population. However, the medicine got a second chance once the companion diagnostics could define HER2 overexpression subgroup in which had much better results. Ildar Akhmetov and Rostyslav Bubnov, Assessing value of innovative molecular diagnostic tests in the concept of predictive, preventive, and personalized medicine, 6(19) EPMA J. 2015, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4588236/. See also, THE CASE FOR PERSONALIZED MEDICINE, 4th edition, Personalized Medicine Coaltion, 2014, 9.

80 Robert Bohrer, Personalized medicines update, Pharmaceuticals Policy, 5 November 2015, available at: http://pharmaceuticalpolicy.blogspot.hk/2014/11/personalized-medicine-update.html#more.

Non-patentability

The court in Mayo Collaborative Services v Prometheus Laboratories, Inc.,[83] clarified that although, method of treatment claims are patentable subject matter in the U.S., the relationship between thiopurine metabolite and the efficacy of the drug is a "law of nature" and therefore excluded from patentability.[84] Following Prometheus, the Court of Appeals for the Federal Circuit revisited this decision in the case Association for Molecular Pathology v Myriad Genetics, Inc.[85] In that proceeding, the Federal Circuit maintained its decision that the method claims with steps that involved "analyzing" sequences and "comparing" them were not patent eligible, but the method for screening potential cancer therapeutics was patent eligible as it involved growing transformed cells and determining the rate of growth of those cells.

Non-novelty

Inherent anticipation should be considered when claiming a method of treatment involving administering a known drug for a known therapeutic purpose based on a previously unknown correlation with a biomarker or group of biomarkers. However, certain factors increase the chance that diagnostics claims are patentable. For example the detection of one of the aforementioned near bioequivalent markers, such as a single nucleotide polymorphism, or adding an active treatment-type step. The claims for diagnostics can have several forms including: a method to determine whether patient with disease X will be responsive to drug Z, comprising detecting biomarker Y and predicting efficacy with Z if Y is present. Citing actual boundaries on the compound administered; the method of administration and dosage can help increase the chances that the claims are accepted by the patent office.[86]

81 Courtenay Brinckerhoff, New USPTO Guidance On Patent Eligibility Of Diagnostic Methods, Pharma Patents Blog, 9 May 2016, available at: https://www.pharmapatentsblog.com/2016/05/09/new-uspto-guidance-on-patent-eligibility-of-diagnostic-methods/.

82 Obviously, the goal of stratified medicine is to provide "the right treatment to the right patients at the right time". See Michael Rugnetta and Whitney Kramer, Paving the Way for Personalized Medicine, Science Progress, September 2009, 3, available at: https://www.scienceprogress.org/wp-content/uploads/2009/09/personalized_medicine.pdf.

83 Mayo Collaborative Services, v Prometheus Laboratories, Inc., supra note 25, 1293.

84 35 U.S.C. § 101. "The LabCorp dissent voices many of the concerns raised by critics of the patent system, arguing that too much patent protection can impede rather than promote progress in science and technology, and attributing an important role to patent eligibility as a gatekeeper to guard against such overprotection." Holman referring to Laboratory Corp. of America Holdings v. Metabolite Laboratories, Inc. 548 U.S. 124 (2006). Christopher Holman, Patent Eligibility as a Policy Lever to Regulate the Patenting of Personalized Medicine (February 18, 2015), in PERSPECTIVES ON PATENTABLE SUBJECT MATTER, edited by Michael Abramowicz, F. Scott Kieff and James E. Daily (Cambridge University Press, 2014), available at: https://ssrn.com/abstract=2566924.

85 Myriad Genetics, supra note 9.

86 Duane Marks, Diagnostic Method Patents, A Framework for Patent-Eligibility of Diagnostic Method Patents post-Mayo, March 20, 2014, available at: https://www.uspto.gov/sites/default/files/patents/announce/may9forum_marks.pdf

5. Conclusions

Pharmaceutical companies standing on the patent cliff, staring in the abyss devoid of future income, become very inventive in finding new medical uses for the known substance, which modestly, by a process of sometimes capricious tinkering with the claim descriptions and sometimes evolutionary refinements, can raise the state of the art. This, again, could evoke Borges' poem The Alchemist:

> "He knows that gold, that Proteus, is lurking
> in all chance happenings, like destiny;
> he knows it hides in the dust along the way,
> in the action of the bow, the arm, the arrow."[87]

Just as the medieval alchemists were not only potterers and bunglers, but, as recent research discovered, in fact proto-scientists,[88] the originator pharmaceutical companies develop a perpetual series of therapeutic and diagnostics patents, based on efficacy studies, which can have real benefits to the quality of patients' lives. For this reason, the Hong Kong government facilitates the legal fiction that first and further medical use claims differentiate from methods of medical treatment and recognizes them as patent-eligible under certain conditions. Another argument for granting patents to these medical use claims is the Lockean "sweat of the brow" rationale: often these incremental innovations only materialize after huge investments.

Governments that are responsible for balancing the interests of patent right holders and the public at large have to take into account what the influence is of relaxing or ignoring the novelty or inventiveness requirements. The slackening of patent standards, which facilitates second and further medical use patents, could stifle generic pharmaceutical companies from manufacturing generic medicines and withhold affordable medicines from the public. Hong Kong has neither a substantial originator nor a generics pharmaceutical industry. It wants to be perceived as a trusted member of the international legal community. Thus it presents itself in the amended patent bill as a staunch protector of intellectual property rights by allowing second and further medical use claims to be patented. However, this decision could only be justified if it also guarantees that only those inventions will be granted a patent if they can prove heightened efficacy or prove that they have the utility as they promised in the claims. One can argue that both these requirements are TRIPS compatible and make use of the flexibilities of for example Article 8 of this treaty.[89] In India, a country with an important generics pharmaceutical industry, Section 3(d) Patents Act describes that new forms of known substances can be granted if an enhanced efficacy can be proved by the patent applicant.[90] In Canada, the doctrine of promised utility ascended. The Court of Appeal in Eli Lilly Canada Inc. v Novopharm Ltd.[91] held that the patent for Olanzapin was invalid as the promised utility that was claimed had not been demonstrated and could not have been soundly predicted. Merges points to the drawback of this approach: the required proof of utility at the filing date deters necessary investment because it delays the award of an exclusive right until a significant amount of money has been spent.[92]

Both aforementioned Indian and Canadian standard enhancers are worth considering for the Hong Kong policy makers. Especially, since they also solve the asymmetric knowledge relation between patent holders and patent office. Without such complementary guarantees, the scales could be tipped in the Hong Kong patent system towards protection of extending originators' interests, while Hong Kong's patients would miss out on affordable medicines. And of course, the Hong Kong courts, also taking the public interest into account, could decide to vary the protection of patent claims according to the level of inventiveness.

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87 Jorge Luis Borges, supra note 1, paragraph 2.

88 "What intrigues Principe and his fellow historians, though, is the growing evidence that the alchemists seem to have performed legitimate experiments, manipulated and analyzed the material world in interesting ways and reported genuine results. And many of the great names in the canon of modern science took note, says William Newman, a historian at Indiana University Bloomington." Richard Conniff, 'Alchemy May Not Have Been the Pseudoscience We All Thought It Was', Smithsonion, February 2014, available at: http://www.smithsonianmag.com/science-nature/alchemy-may-not-been-pseudoscience-we-thought-it-was-180949430/#iwZgyYdHqXP3WziY.99.

89 Article 8(1) TRIPS: "Members may, in formulating or amending their laws and regulations, adopt measures necessary to protect public health and nutrition, and to promote the public interest in sectors of vital importance to their socio-economic and technological development, provided that such measures are consistent with the provisions of this Agreement."

90 Ali, supra note 23, 96.

91 Eli Lilly Canada Inc. v Novopharm Ltd., 2012 FCA 232.

92 See Robert Merges, Expert Report in the Arbitration under the Arbitration Rules of the United Nations Commission on International Trade Law and the NAFTA (Case No. UNCT/14/2), Eli Lilly and Company v Government of Canada, 29 September 2014, available at: http://www.italaw.com/sites/default/files/case-documents/italaw4141.pdf. See all documents submitted for this case, ICSID, Case Details, available at: https://icsid.worldbank.org/en/Pages/cases/casedetail.aspx?CaseNo=UNCT/14/2.
"Firms that seek venture-funding appear to be patenting more actively prior to the funding event (and for the purpose of securing funding), and venture-capital investors appear much less willing to fund companies that hold no patents." Stuart J.H. Graham, Robert P. Merges, Pamela Samuelson, and Ted Sichelman, High Technology Entrepreneurs and the Patent System: Results of the 2008 Berkeley Patent Survey (2009) 24 BERKELEY TECH. L.J. 1255, 1280.

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Dr. Tam is CEO/Chairman of DiagCor Bioscience Inc Ltd. He received his Ph.D. (UCD); BSc. (CUHK) in physical chemistry. Dr. Tam has spent 30 years teaching and research in biochemistry and molecular biology in HK and USA. He was the co-founder, secretary, president of the Hong Kong Biochemistry Association. During his tenure in HKU, he brought in the Cutting-edge rDNA technology and trained many regional scientists in 1983, by organizing the 1st International rDNA Training Course. His laboratory has cloned the globin, G6PD and Insulin receptor genes; uncovered mutations responsible for genetic diseases. After retirement, he stayed in Hong Kong and co-founded 3 biotechnology companies, providing the platform for young scientists to continue work in the field. Dr. Tam had been Visiting Professor at UCSF, Baylor Medical College and Augusta College of Medicine and Visiting Scientist of NIH and R&D Director, EY Laboratories Inc. He is the inventor of over 10 international patents and the Flow-through Hybridization technology has become the core technology for many companies in Europe and greater China, including DiagCor Bioscience Ltd.

Cesar Wong Sze Chuen

Cesar Wong, Ph.D., FFSc (RCPA), is currently an Associate Professor in the Department of Health Technology and Informatics, Faculty of Health and Social Sciences, the Hong Kong Polytechnic University. Dr. Wong is also the Honorary Professor in the Department of Molecular Imaging, Faculty of Medicine, Zhejiang University, China; Adjunct Associate Professor in the Department of Clinical Oncology and the School of Public Health and Primary Care, Faculty of Medicine, The Chinese University of Hong Kong. Besides, he is the Founding Fellow of the Faculty of Science, The Royal College of Pathologists of Australasia due to his continuous contribution in Anatomical and Molecular Pathology. His main research interest is to develop tumor markers especially on circulating tumor cells and plasma RNA for diagnosis, prognosis of Asian common cancers such as colorectal cancer, nasopharyngeal cancer and cervical cancer. He has over 95 peer-reviewed publications and more than 60 abstracts. He has been publishing in prestigious journals such as Annals of Oncology, Clinical Cancer Research, Oncogene, Biosensors and Bioelectronics, American Journal of Pathology, Journal of Pathology and Clinical Chemistry. He succeeded in obtaining a number of competitive Research Grants in Hong Kong including the Hong Kong Collaborative Research Fund, General Research Fund, Health and Medical Research Fund, Hong Kong Anti-Cancer Society Novel Research Grant and he is an editorial board member of 25 peer-reviewed journals. Besides actively involving in molecular detection of tumor markers, Dr. Wong is also appointed as the scientific assessor in the Hong Kong Laboratory Accreditation Scheme in Molecular and Anatomical Pathology.

Ka Wai Wong

Dr. Wong received the B.Sc., M.Phil. and Ph.D. degrees in chemistry from the Chinese University of Hong Kong (CUHK) in 1992, 1995 and 1999, respectively. After graduation, he joined the Advanced Surface and Materials Analysis Centre as Laboratory Manager and then joined the Department of Physics of CUHK, as Postdoctoral Fellow with major research focus on organic/polymeric optoelectronics. From 2003 to 2005, he worked at a biotech company in Hong Kong as a Project Manager leading a R&D team on developing novel CMOS-based DNA chips for molecular diagnostics. He then joined the Department of Physics at CUHK, the Green Energy and Green Manufacturing Technology R & D Centre in Chengdu, the Department of Chemical and Biomolecular Engineering of Hong Kong University of Science and Technology as research faculty. Also, he is the co-founder of HL Science & Technology Limited and ASMAC Ltd. His major research interests include surface science, sensing technology, nanotechnology, and materials engineering.

Samantha Yung

Samantha moved back to Hong Kong from Colorado, where she was trained as a biologist with a focus on biomedical and pre-veterinary sciences at Colorado State University. Before joining Hong Kong Science and Technology Parks, she has dedicated her time in treating marine mammals and advocating animal welfare at Hong Kong Ocean Park and HKSPCA. At the same time, Samantha has also started a business venture targeting the robust biomedical start-up community, provocatively seeking innovative biomedical solutions to bring about technological advancement in our daily lives. The company has secured orders with clients like the Hong Kong Jockey Club and other veterinary clinics within the first quarter of establishment. Currently, Samantha is working at the Biomedical Technology Cluster in Hong Kong Science & Technology Parks Corporation, where she helps manage molecular diagnostics and therapeutic company accounts, direct and lead projects for biomedical events and conferences, support business development for bio-incubates and provide other administrative and business support services.

Sherman Zheng 郑勋华 博士

郑勋华博士1946年出生于中国，1970年广州中山医学院本科毕业，曾任十年全科医生，后有二年回到中山医学院附属医院普通外科任职外科医生。八十年早期到美国深造，于1991年获得美国纽约大学(NYU)生物化学博士学位，并继续博士后的研究工作，重点在生物膜和蛋白质生物学、免疫学、和分子基因工程的研究。1989年到1994年在美国长岛UBI（United Biomedical Inc）公司作为研究员从事人工合成基因来发展艾滋病疫苗的研发工作，同时也研制对各种外源性病菌的临床分子诊断药箱。1995年回到美国纽约大学医学中心血液病理,分子诊断实验室任负责人，在分子水平上设计用分子生物学的技术检测血液病中癌症的特征和分型以及癌前期各种主要的标记物。特别在淋巴瘤和白血病的基因重组及癌变的研究。是美国早期运用核糖核酸扩增方法从事血液肿瘤临床分子诊断的专家之一，并一直在该医院进行临床第一线的诊疗和科研工作了二十多年，也经常参与美国临床分子病理医生的培训工作。2015年受香港新亚医学科技有限公司（PANGENIA LIFESIENCES LTD）和广州百皋医学检验所有限公司聘请为资深顾问，现任健港生命科技国际有限公司科技总监。也利用良好的教育背景、多年的医学临床经验、将中西方科学研究知识和在生物科技公司的工作经验再投身到大健康产业的开发中。

About the publisher

Started in 1998 by Dr. Albert Wai-Kit Chan, United States-China Intellectual Property Institute (USCIPI) is dedicated to promoting the education of intellectual property concepts and legal matters of both China and the United States. Hoping to serve as a bridge between the two countries, USCIPI supports and hosts meetings, training courses, seminars, and conferences that are open to all participants, including government officials, scholars and business people. Another major focus is producing relevant literature as another medium to propagate information and knowledge. After a period of dormancy, USCIPI is happy to announce that it has reactivated with the publication of this second volume of Biotechnology in Hong Kong.

OUR MISSION

United States-China Intellectual Property Institute (USCIPI) is a non-profit organization devoted to promoting the mutual understanding of intellectual property practices in the U.S. and China. Our philosophy is "We Educate. We Serve. We Bridge." We hope our work will help minimize intellectual property disputes between the U.S. and China in order to bring about both countries' innovative excellence and maximize collaborative opportunities.

OUR METHOD

We are dedicated to educating those interested in learning about intellectual property concepts and legal matters of both countries. Hoping to serve as a bridge between the U.S. and China, we invite government officials, scholars and business people of both countries to come together at our meetings, training courses, seminars, and conferences.

About the Editor

Dr. Albert Wai-Kit Chan is a former research scientist in molecular biology. He was born and raised in Hong Kong, graduated from The Chinese University of Hong Kong, and was awarded his Ph.D. in virology at Baylor College of Medicine in Houston, Texas. Dr. Chan then completed his postdoctoral training at Cold Spring Harbor Laboratory in New York as an American Cancer Society postdoctoral fellow. With the emerging legal needs of the biotechnology industry in the late 1980s, Dr. Chan organically began his career in law, focusing on intellectual property and using his background in science as a solid foundation for his practice. He later received his J.D. degree from Columbia University School of Law in New York.

Through the years, Dr. Chan has handled all areas of intellectual property law, including technology transfer, patents, trademarks, copyrights, business transactions, and trade secrets. He is well-versed in all aspects of prosecution and litigation and is experienced in licensing, technology transfer and the evaluation of intellectual property portfolios. Dr. Chan has served as an adjunct professor of law at The City University of New York School of Law, where he taught intellectual property law, patent law, technology transfer, Internet and the law, food and drug law, and international business law. He is currently adjunct associate professor in the School of Life Sciences at The Chinese University of Hong Kong and has adjunct professorship in the Department of Health Technology and Informatics at The Hong Kong Polytechnic University.

Dr. Chan has worked extensively with all constituents of the intellectual property protection process in the U.S., China and other international jurisdictions. The importance of intellectual property protection for, not only businesses but also for, the overall national economy became apparent. With all the IP and transactional work he has done in China, which includes facilitating joint ventures and contracts between East and West companies and building up clients' intellectual property portfolios, one thing became clear: Intellectual Property was a mystery to many people. Not only that, differences in cultures and constant changes in local laws and practices made it difficult for even those who are considered experts in the field to navigate. There was a need to gather to communicate, share perspectives and educate. With this in mind, the United States-China Intellectual Property Institute was founded.

Dr. Albert Wai-Kit Chan is a partner of the Law Offices of Albert Wai-Kit Chan, PLLC in the New York. Dr. Chan also heads Albert Wai-Kit Chan Intellectual Property Limited in Hong Kong.