Cancer Taskforce Report

Contents

A. AIM

1. This report details the analysis and recommendations of the Cancer Taskforce (CTF). It reviews both global and local cancer research landscapes and identifies Singapore's current strengths, challenges and potential areas of growth. The report recommends three themes in cancer research for the Open Fund Large Collaborative Grants (OF-LCGs). Lastly, the report proposes a five-year research roadmap as well as recommendations to overcome roadblocks that may impede the development of cancer research in Singapore.

B. BACKGROUND

2. Cancer is a highly prevalent disease around the world, including in Asia and Singapore. The Singapore Burden of Disease (SBoD) 2010 report published by MOH in 2014 reported the following:

(a) The burden of disease and injury resulting from premature mortality and disability was 399,675 disability-adjusted life years (DALYs) in Singapore in 2010 (i.e. 106 DALYs lost per 1,000 resident population). Cancers were responsible for 18.9% of total DALYs (Figure 1).
(b) Between 2004 and 2010, there was a 12.7% increase in cancer burden: 29.8% increase in disability burden and 11.4% increase in premature mortality burden. Crude cancer burden per head of population rose by 4.2%. Age-standardised cancer burden per head of population, however, decreased by 8.0%. In 2010, 82% of cancer burden were from premature mortality.
(c) Lung, breast, and colon and rectum cancers were the leading specific causes of cancer burden, which were also ranked 6th, 9th and 11th in overall DALYs respectively (Table 1).

3. The Singapore Cancer Registry Annual Registry Report – Trends in Cancer Incidence in Singapore 2010-2014, published by the National Registry of Diseases Office (NRDO) in March 2016, described the incidence, mortality and survival of cancer cases between 2010 and 2014, with a focus on seven selected cancers, namely breast, cervical, colorectal, ovarian, uterine, prostate and lung cancers.

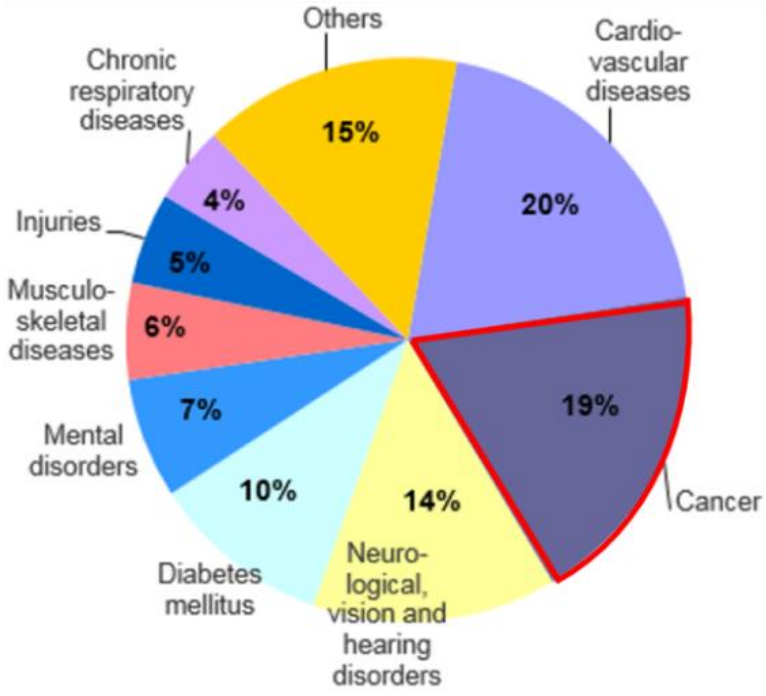
(a) Among males, colorectal, lung, and prostate cancers were the three leading cancers diagnosed. Among females, breast, colorectal, and lung cancer were the three most frequently diagnosed cancers.
(b) In terms of prevalence[1] among males, colorectal cancer accounted for the largest proportion of the 2-year prevalent cases, followed by

[1] **Prevalence** represents new and extant cases alive on a certain date, in contrast to incidence which reflects new cases of a condition diagnosed during a given period of observation. Prevalence is a function of both the incidence of the disease and survival, and is useful in ascertaining the burden of cancer on the healthcare system. **2-year prevalence** was estimated by counting the number of invasive primary cancers diagnosed from January 1, 2013 to December 31, 2014 in persons who were still alive on January 1, 2015. Similarly, **5- and 10-year prevalence** estimates were based on cases diagnosed since January 1, 2010 and January 1, 2005 respectively. The prevalence proportions (per 100,000) were obtained by dividing the prevalent counts by the population on January 1, 2015 and multiplying by 100,000. Limitation: The prevalence figures do not take into account the possibility that prevalent cancer cases may be in remission. In the statistical sense, it means that

prostate and lung cancers. However, the prevalence of lung cancer dropped from third highest at 2 years, to fifth highest at the 5- and 10-year marks, while prostate cancer consistently retained its second place. This is likely due to the low survival rate among lung cancer patients in general and that there is no effective screening modality for lung cancer, on top of the better survival prognosis for prostate cancer. Liver and stomach cancers ranked lower in prevalence compared to incidence for the same reason of low survival rate.

(c) For prevalence among females, breast, colorectal, and uterine cancers retained their respective ranks (1 through 3) regardless of the duration of the observation period for prevalence. However, as with males, the ranking of the prevalence of lung cancer also decreases with time, dropping from the fourth position at the 2-year mark to ninth at 10 years. The prevalence rank order of the other cancers, on the other hand, remained the same otherwise.

Figure 1. DALYs by Broad Cause Group Expressed as Proportions of Total, 2010 (Source: Singapore Burden of Disease Study (SBoD) 2010, MOH)



these cases attain the same mortality rate as the general population. The inclusion of remission cases in prevalence count overestimates the actual prevalence, though this inflation is minimal.

Table 1. The Twenty Leading Specific Causes of DALYs, 2010 (overall and by gender) (Source: SBoD 2010, MOH)

Rank	Overall (DALYs = 399,675)	% of Total	Males (DALYs = 210,267)	% of Total	Females (DALYs = 189,408)	% of Total
1	Ischaemic heart disease	10.4	Ischaemic heart disease	12.6	Diabetes mellitus	10.6
2	Diabetes mellitus	10.4	Diabetes mellitus	10.1	Ischaemic heart disease	8.0
3	Stroke	6.8	Stroke	7.4	Stroke	6.2
4	Vision disorders	4.4	Lung cancer	4.4	Breast cancer	5.8
5	Alzheimer's & other dementias	3.9	Vision disorders	4.0	Vision disorders	4.9
6	Lung cancer	3.4	Chronic obstructive pulmonary disease	3.2	Alzheimer's & other dementias	4.9
7	Adult-onset hearing loss	3.0	Alzheimer's & other dementias	2.9	Rheumatoid arthritis	3.3
8	Lower respiratory tract infection	2.8	Colon & rectum cancer	2.8	Adult-onset hearing loss	3.2
9	Breast cancer	2.7	Adult-onset hearing loss	2.7	Lower respiratory tract infection	3.0
10	Schizophrenia	2.7	Lower respiratory tract infection	2.7	Schizophrenia	2.9
11	Colon & rectum cancer	2.6	Schizophrenia	2.4	Colon & rectum cancer	2.5
12	Rheumatoid arthritis	2.4	Self-inflicted injuries	2.1	Lung cancer	2.4
13	Chronic obstructive pulmonary disease	2.1	Liver cancer	2.1	Anxiety & depression	2.4
14	Self-inflicted injuries	1.8	Road traffic accidents	1.7	Nephritis and nephrosis	1.6
15	Anxiety & Depression	1.7	Autism spectrum disorders	1.7	Osteoarthritis	1.5
16	Osteoarthritis	1.5	Rheumatoid arthritis	1.6	Self-inflicted injuries	1.4
17	Liver cancer	1.5	Mouth & oropharynx cancer (including Nasopharynx)	1.5	Ovary cancer	1.0
18	Nephritis and nephrosis	1.5	Osteoarthritis	1.5	Falls	1.0
19	Autism spectrum disorders	1.3	Falls	1.3	Asthma	0.9
20	Road traffic accidents	1.2	Nephritis and nephrosis	1.3	Stomach cancer	0.9
% DALYs accounted for by the top 20 specific causes		68.0		70.2		68.3

Note: Total may not add up due to rounding

C. CURRENT LOCAL CANCER RESEARCH LANDSCAPE

Basic cancer research

4. Basic cancer research is mainly conducted in the universities (National University of Singapore (NUS), Nanyang Technological University (NTU), Duke-NUS Medical School (Duke-NUS)) and A*STAR research institutes. A*STAR research institutes themselves have more than 80 groups of researchers working in the cancer field (basic and translational research). There are also several major research laboratories in the public health institutes (PHIs) and academic medical centres (AMCs) working on basic cancer research, such as the National Cancer Centre Singapore (NCCS), National University Cancer Institute, Singapore (NCIS), National University Hospital (NUH), Singapore General Hospital (SGH), National Neuroscience Institute (NNI) and Tan Tock Seng Hospital (TTSH).

Translational and clinical cancer research

5. Translational and clinical cancer research is conducted in the universities, A*STAR research institutes and the PHIs. However, human subject related clinical research and clinical trials are conducted in the PHIs. The clinical trials are coordinated and supported by the institutional clinical trials units, IMUs established at SingHealth and National University Health System (NUHS), and by Singapore Clinical Research Institute (SCRI).

6. There are capabilities in cancer-related drug development in the A*STAR Experimental Therapeutic Centre (ETC) and associated Drug Discovery & Development (D3) unit. Together, ETC/D3 provide guidance on early stage scientific discoveries and capabilities to proof-of-concept in man. The goal is to translate scientific discoveries into diagnostics and research tools, contributing to the pipeline of drug compounds for late-stage clinical trials.

Health Services Research (HSR)

7. There are several groups which are working on HSR, which is inter-disciplinary and trans-disciplinary with the rest of the cancer research groups.

(a) Saw Swee Hock School of Public Health (SSHSPH) in NUS focuses on translational public health research and methodological capabilities, epidemiology on breast cancer, biostatistics and modelling, and health systems and behavioural sciences;
(b) Lee Kong Chian School of Medicine (LKC) in NTU has a Health Systems and Population Health theme; and
(c) Duke-NUS's signature research programmes include health services and systems research and the Lien Centre for Palliative Care.

Cancer cohorts and research networks

8. A number of cohorts/research networks that can facilitate cancer research have been assembled over the years. These are for different cancer types focusing on various aspects such as clinical trials, cohort studies and epidemiological studies of social and risk factors. They are set up and driven by clinicians and PHIs for their research and are either run independently by the clinicians or are supported/coordinated by SCRI.

Cancer tissue repositories

9. Currently, there are a few tissue repositories and registries. These resources, together with collaborations and data from the National Registry of Diseases Office (NRDO), are provided to the users.

(a) NUH Tissue Repository (TR) and Hospital-based Cancer Registry (HCR);
(b) SingHealth Tissue Repository; and
(c) National NNI Brain Tumour Resource (comprises patient-derived cell lines, their matched animal xenografts and original primary tissue).

Other infrastructure

10. NCCS and NUH each has a GMP facility which has facilitated the growth of immunotherapy trials and research. The recently established SingHealth/Duke-NUS Institute of Precision Medicine (PRISM) seeks to improve patient outcomes by identifying patient populations that are likely to benefit from specific treatments, while avoiding treatment-related toxicities. It provides a common platform to share the knowledge and experiences in both biomedical discovery and clinical implementation by generating databases and toolkits to drive impactful translational research further. It will also play a coordinating role in managing ground-up grant calls from SingHealth and Duke-NUS related to precision medicine, to provide seed funding for novel, promising ideas.

Human talent

11. Singapore has a significant number of researchers working in cancer. The percentage of clinician scientists focusing on cancer research is also the highest, at about 28% of the total clinician scientists in Singapore.

Achievements

12. The cancer research in Singapore has yielded numerous achievements in terms of scientific advances, publications, health and economic outcomes. The consistent and exceptional growth in volume of publications is an indication that the intellectual output from the cancer research initiatives/programmes in the

institutions are on track. There are a total of 2,300 publications on cancer research from Singapore in the past four years (from 2013 – 2016). Many of the research efforts had also led to collaborations with local and international industry partners; these included but are not limited to, Bristol-Myers Squibb, Clearbridge BioMedics, Eli Lilly and Company, GlaxoSmithKline, HistoIndex, Ipsen, MSD International, Roche, Servier, Tessa Therapeutics, Aslan, Chugai and etc. A number of clinical cancer research carried out in Singapore have also made substantial impact. For example, through the Singapore Gastric Cancer Consortium funded by the NMRC TCR Flagship Programme, researchers developed a novel flexible endoscopic robotic system that enables intricate surgical procedures to be performed without the need for external incisions. The surgical system enabled the world's first human clinical test of endoscopic colorectal cancer removal in Singapore in September 2012. In another example, ETC and D3, in collaboration with Duke-NUS, discovered and developed ETC-159, Singapore's first publicly-funded anti-cancer drug. ETC-159 entered phase 1 clinical trials in June 2015.

D. INTERNATIONAL CANCER RESEARCH LANDSCAPE

13. Globally, cancer is a heavily invested field of research. There are numerous organisations, ranging from public institutions to non-profit organisations and privately companies dedicated to cancer research. Some of the more prominent and/or recent initiatives are listed below:

(a) Provocative Questions (PQ) Initiative by the National Cancer Institute (NCI);
(b) International Cancer Genome Consortium (ICGC);
(c) The Cancer Genome Atlas (TCGA);
(d) Cancer Moonshot by NCI;
(e) Cancer Moonshot 2020;
(f) Parker Institute for Cancer Immunotherapy (PICI);
(g) Bloomberg-Kimmel Institute for Cancer Immunotherapy;
(h) Cancer Research UK – Grand Challenge Awards; and
(i) SCRUM-Japan

E. INDUSTRY INTEREST AND ECONOMIC OPPORTUNITIES

Global

14. The global oncology drug market (therapeutics and supportive drugs) was valued at US$107 billion in 2015, an increase of 11.5% over 2014 (on a constant dollar basis) and up from US$84 billion in 2010, as measured at invoice price levels[2]. The annual global growth rate is expected to be in the 7.5-10.5% range through 2020, exceeding US$150 billion by 2020. Much of the growth would be driven by the wider utilisation of new products, especially immunotherapies.

[2] Global Oncology Trend Report: A Review of 2015 and Outlook to 2020 (IMS Institute for Healthcare Informatics)

15. The number of drugs in the R&D pipeline with a cancer focus has increased by 15.9% to 4176 in 2016[3]. In other words, 30.4% of all drugs in development have an oncological target. The growth is mostly attributed to the rise of the immuno-oncology field. Specifically for oncology drug development, there are more than 500 companies developing almost 600 late-phase therapies, with more than 300 of them having R&D pipelines exclusively focused on oncology. Collectively, cancer therapies make up 49% of the R&D activity of the companies. Fifteen of the top 25 disease focus of pharmaceutical companies are cancer indications; the top five cancer indications are non-small cell lung cancer, breast, pancreatic, ovarian and colorectal cancers.

16. In terms of modalities, late-phase oncology R&D activity remains concentrated on targeted therapies, including small molecule protein kinase inhibitors and biologic monoclonal antibodies (87% of late-phase pipeline). In particular, there are increasing focuses on targeted therapies that use gene marker tests to indicate likelihood of tumour response, or amplify patient's own immune response to target the cancer.

Local

17. Over the past few years, the Singapore cancer research community has had numerous discussions with various companies, some of which culminated in research collaborations and partnerships. The clinical cancer community has also actively conducted both company-sponsored trials as well as investigator-initiated trials.

F. SELECTION OF RESEARCH FOCUS AREAS

18. In order to fulfil the HBMS' objectives to excel in areas where Singapore has the potential to be differentiated and internationally-competitive, there is a need to maximise the use of research funds by focusing on specific cancer research areas that could potentially have the greatest impact. The CTF noted that there was a need to have a fine balance between local and international impact, as well as amongst scientific, health and economic impact.

19. The CTF took the approach of mapping the cancer research in Singapore based on the journey of a cancer patient – from early diagnosis of cancer to early management of the disease, and finally post early management, when a patient progresses to the advanced stage. In addition, the CTF took into consideration the latest technology developments which have the potential to disrupt the cancer field, as well as subject matters that might have been traditionally overlooked by the cancer research community but have the potential to impact cancer healthcare. Correspondingly, the CTF brainstormed around the following five thematic areas:

(a) Prevention and precision detection;

[3] Pharmaprojects, January 2016

(b) Mechanism of tumourigenesis;
(c) Metastasis and resistance;
(d) Cancer Immunology; and
(e) Social science/public health to improve cancer outcomes.

20. Recognising the complex field of cancer research and the numerous angles by which cancer research could be pursued, the CTF also identified several recurring focus areas that should integrate across the five themes when being evaluated:

(a) Analytics;
(b) Behavioural sciences;
(c) Best care for cancer patients;
(d) Clinical trials;
(e) Cost-effectiveness;
(f) Experimental therapeutics;
(g) Financing;
(h) Imaging;
(i) Model systems; and
(j) Precision medicine.

21. Following the selection of the research focus areas, a cancer workshop was held to engage the wider cancer research community. The community took into consideration several factors such as the availability of local expertise and capabilities, gaps in scientific knowledge, scientific importance, and potential impact. The CTF also further sought inputs from the community subsequently via an email survey on the research topics that they would be keen to either participate or lead as part of a large collaborative programme.

G. RECOMMENDED RESEARCH PRIORITY AREAS FOR OPEN FUND-LARGE COLLABORATIVE GRANT (OF-LCG)

22. For the OF-LCG call, the CTF recommends three priority themes:

(a) Precision methods for prevention, disease detection, and treatment stratification.

Focus	To reduce preventable cancers(s) and optimise treatment for cancer patients in Singapore.
Challenge Statement	To utilise basic, translational, clinical and implementation science approaches to enable the identification of at-risk individuals, early detection of cancer and stratification of cancer treatment (e.g. through the identification of biomarkers). Due consideration should be given to the cost-effectiveness of the approaches, and the attractiveness of such approaches to industry. This is in

	support of long-term goals of reducing the national incidence of late-stage cancer by 10% by 2025, and increasing the survival rate of cancer patients in Singapore by 20% by 2030.
Rationales	<u>Prevention</u> Research suggests that only five percent of cancers are hereditary[4]. In other words, non-inherited causes of cancers such as lifestyle choices, foods and physical activity levels can have a direct impact on the overall cancer risk. While several cancer risk factors are known, better deployment of the relevant interventions are necessary to bring about significant impact to Singapore in terms of health and social outcomes. There also remains some potential for the discovery of new biomarkers and interventions that could lead to scientific excellence and talent development. However, industry interest in this area is scarce as companies are traditionally in the business of treating, as opposed to preventing, diseases. <u>Early Detection</u> Many patients whose cancers are detected and treated early have better long-term survival than patients whose cancers are not found until symptoms appear. Unfortunately, effective screening tests for early detection do not exist for many cancers, and many of the available tests have not proven effective in reducing cancer mortality. <u>Treatment stratification</u> The IMS Institute for Healthcare Informatics expects cancer treatment costs to hit US$150 billion by 2020, up from US$107 billion in 2015. This is, in part, due to the rising cost of anti-cancer drugs. For instance, Yervoy (Bristol-Myers Squibb) that was approved by FDA for the treatment of metastatic melanoma, costs US$120,000 for just four doses and is only effective for a small population of cancer patients. While it is not ethically possible to stop the use of these innovative drugs in Singapore, better biomarkers to identify the relevant patient population that would most likely respond to these expensive treatment could avoid unnecessary use of drugs and hence alleviate the rising healthcare burden in Singapore. The industry has also taken the

[4] http://preventcancer.org/learn/preventable-cancers/

	same approach to address concerns regarding the high cost of drugs. Biomarkers research is, therefore, an area of immense academic interest and of great potential for impact to Singapore in terms of healthcare and economic outcomes.

(b) Metastasis and resistance

Focus	To develop novel understandings of and therapy for Asia-prevalent cancer.
Challenge Statement	To utilise basic, translational, clinical and implementation science approaches to understand the major factors mediating drug resistance and metastasis, and develop novel therapy to mitigate them so as to improve the survival of cancer patients. Due consideration should be given to the cost-effectiveness of the approaches, and the attractiveness of such approaches to industry. This is in support of the long-term goal of increasing the survival rate of cancer patients in Singapore by 20% by 2030.
Rationales	The issues of metastases and drug resistance has plagued the cancer field for decades, with limited availability of effective known interventions. Unlike in the past, researchers are now equipped with better scientific understanding and technologies. Specifically in the case of Singapore, the availability of human talents with deep and broad expertise, coupled with a world-class infrastructure enabling bench to bedside research, puts Singapore in a competitive position to lead in this area of research. Consequently, there are immense opportunities for both local and global impact in terms of healthcare, scientific and economic outcomes

(c) Enhancing cancer immunotherapy

Focus	To improve outcomes of Asia-prevalent cancers using immunotherapeutic approach.
Challenge Statement	To utilise basic, translational, clinical and implementation science approaches to improve patient selection for immunotherapy, so that patients receive maximum benefit from the therapy (e.g. through the development of new targets for immunotherapy or overcoming resistance). Due consideration should be given to the cost-effectiveness of the approaches, and the attractiveness of

	such approaches to industry. This is in support of the long-term goal of increasing the survival rate of cancer patients in Singapore by 20% by 2030.
Rationales	Immunotherapy has been one of the biggest disruptors to the cancer treatment world. Stories about new immunotherapies offering renewed hope where not too long ago there was none, abound these days. The promise of cancer immunotherapy has also caused many pharmaceutical companies to get on board and invest heavily in cancer immunotherapy treatments. Of note, the market was estimated to be valued at US$25 billion to US$40 billion by the end of the next decade (estimates based on the current size of the market and the potential for immunotherapy to gain as much as a 50% share of the oncology market)[5]. There is no doubt that this field is highly competitive, especially with the massive public and private investments. Nevertheless, the field is here to stay and it would be critical for Singapore to stay competitive and relevant, or risk becoming obsolete from the rest of the world. Notably, cellular therapy requires well established teams that work well together in a protocol, with close handling of products from isolation of cells, purification and expansion, manipulation, to packaging and administration. This is technologically challenging and poses safety challenges, hence no country in Asia has a foothold yet. Therefore, this is an opportunity for Singapore, with its well-developed scientific teams, well-trained physicians and sophisticated hospital infrastructure, to take a lead and establish a brand.

23. The CTF felt that there is potential to engage health economists to perform additional health economic analyses to complement the research. These analyses could include:

(a) Burden of illness studies to help understand which cancer types impose the largest economic burdens in Singapore. The economic burdens may include, but are not limited to, medical costs, productivity losses, caregiver burden, the value of premature mortality, or quality-adjusted life years (QALYs) lost. This would complement traditional epidemiological studies on disease burden;

[5] http://www.investopedia.com/articles/investing/082013/will-immunotherapy-disrupt-oncology-market.asp

(b) Health economic studies, both early and late stage to quantify the incremental cost effectiveness of selected therapies. This would allow for quantifying whether the benefits gained from the interventions are worth the additional costs. Policymakers can compare the results to standard thresholds for cost-effectiveness and use these results for decision making to approve a certain technology and/or subsidizing its cost; and

(c) Budget impact analyses that show the net costs resulting from adoption of a new technology. Although interventions that improve health are unlikely to save money on net, they do have economy wide effects that suggest some "winners" and "losers". Health economic analyses can help elucidate understanding of the incidence of costs and benefits, and the net impacts on society that result from adoption of new technologies.

24. As a general guideline, the CTF recommends focusing on cancers that Singapore has a strong track record in, as well as cancers with important public health impact to Singapore. Notably, the CTF is cognisant that Singapore is strong in Asian-prevalent cancers, but the scale of Singapore's research could be easily overshadowed by the regional countries. In addition, the CTF recognised that research on rarer cancers has the potential to impact scientific excellence in terms of better understanding of disease pathogenesis, and that prioritising cancers in which early detection can truly make a difference could allow faster healthcare impact to be realised.

25. Taking all the factors listed above into considerations, the CTF proposes to prioritise on lethal cancers and/or cancers with Asian phenotype, in particular on six cancer types: lung cancers, breast cancers, liver cancers, gastrointestinal cancers, nasopharyngeal cancers and haematological malignancies.

H. FIVE-YEAR ROADMAP FOR CANCER RESEARCH

(I) RESEARCH PRIORITY AREAS

26. According NCI, there are more than 100 types of cancer based on the organs or tissues where the cancers form and the type of cells that form cancers[6]. This does not take into account the further sub-classifications of each cancer type, which often have substantial differences in terms of natural histories and molecular mechanisms that would require different treatment strategies. Juxtaposed against the nature of research, i.e. basic, translational and clinical, as well as the modalities/technologies, e.g. imaging system, analytics, animal models, one can only begin to appreciate the magnitude of the research work that falls under the umbrella of the cancer field.

27. With a long-term vision to enable early detection of cancer and to enhance the prognosis and life expectancy of cancer patients, the CTF devised a

[6] https://www.cancer.gov/about-cancer/understanding/what-is-cancer

preliminary roadmap articulating the broad research focus, desired goals, Singapore's competitive advantage, as well as roadblocks and potential solutions for cancer research in Singapore. Briefly, the CTF has identified 10 broad focus areas based on the initial five thematic areas (Para 19).

Broad Research Focus

28. Prevention of cancer – to reduce modifiable cancer risk factors. There are many known modifiable risk factors of cancers, such as tobacco and alcohol use. Research indicates that over half of all cancers in developed countries could be prevented if the appropriate population-wide measures are implemented[7]. These include lifestyle modification, surveillance to drug re-purposing such as aspirin and metformin to reduce cancer risk. The most powerful example is the reduction of overall lung cancer mortality in many countries through the reduction of smoking in the population through largely national public health policies. The CTF is of the view that this is a crucial national imperative and requires multi-agency interventions.

29. Cancer Screening – to improve uptake, literacy and the role of primary care, and to improve participation of cancer screening. Cancer screening is challenging globally as it involves testing asymptomatic population for signs of disease. This allows the opportunity to detect cancers during the early stages, therefore reducing healthcare burden as later-stage cancers are usually harder to treat and involves more extensive and costly treatments. A recent study commissioned by Cancer Research UK modelled the costs of treating bowel, ovarian and lung cancers when diagnosed at different stages; the results demonstrated that treatments for late stage (stage 3/4) cancers cost the National Health Service (NHS) nearly 2.5 times the amount spent on early stage (stage1/2) services[8]. The CTF is of the view that the Singapore population may be more compliant and would be well placed to fare well if the screening programmes are tailored to the cultural and behavioural patterns of the population.

30. Early Detection – to set up a cohort platform to support the development of biomarkers, to understand and reduce the lifetime risk for cancer, and to incorporate health economics/cost-effectiveness studies. Due to the ease of measurement, biomarkers have been evaluated as screening/diagnostic tests for malignancy. However, many still face issues such as the lack of sensitivity and specificity, suggesting the need to identify better biomarkers. Such work usually involves large cohort studies, which are prohibitively expensive, long term projects and resource-straining to conduct. Nevertheless, Singapore's manageable size and efficient and systematic ability to collect and coordinate data across the country may make it feasible for conducting such studies.

[7] Stein, C. J., and Colditz, G.A., (2004). Modifiable risk factors for cancer. Br J Cancer. 90(2):299-303

[8] http://scienceblog.cancerresearchuk.org/2014/09/22/saving-lives-and-averting-costs-the-case-for-earlier-diagnosis-just-got-stronger/

31. In general, the CTF felt that this is a relevant area of investigation, especially with the -omics companies developing much cheaper gene sequencing and protein array platforms. For instance, Illumina just announced a US$100 rapid full sequencing capability and other companies such as GRAIL are fully focused on cutting edge liquid biopsies. Additionally, Hong Kong is embarking on a more than 20,000 normal volunteer longitudinal study to detect early NPC via cell-free DNA technology. Then again, the CTF noted that there have been very few biomarkers at the omics level to have made a survival gain in cancer mortality through early detection.

32. It should also be recognised that there is already proliferation of cohort studies ongoing in Singapore, and that the situation is likely to lead to fragmentation and lack of data integration between cohorts. At the same time, it is difficult to mandate the cessation of small cohort studies, as investigators are often able to tap into multiple funding streams to support such initial studies.

33. Drugging the "undruggable" – to develop therapeutics for difficult targets. This is a challenging research area and mainly the domain and strength of the industry. Many attractive and validated cancer targets are described as "undruggable" and remains outside the reach of pharmacological regulation. One such example is TP53, the most frequently mutated gene in cancer. However, with the advancement of research and advent of new technologies, researchers are beginning to grapple with previously "undruggable" targets. The CTF noted that potential promising platforms are emerging in Singapore, e.g. in protein chemistry, antibody technology and development. One such example is Sir David Lane's team looking at stapled peptides as a novel class of drug for cancer therapy.

34. Tumour as a tissue – to determine how cancer cells hijack the microenvironment to drive progression in different tumour types. This is currently an area of intense research, although largely ignored and underestimated over five years ago. There is a need for a better model to understand the microenvironment related to the niche, as well as the immune environment. The study of human samples should not be limited to tumour cells, but to look at the changes to the environment, including the changes induced by the cancer cells itself. Similarly, the effect on therapeutics may be mediated partly through changes induced in the microenvironment by the treatment.

35. Early events in tumour initiation – to understand non-genetic events e.g. inflammation, viral infection and proteomic alteration. This is a very important field of cancer research. There is a need for models to study this area. Identification of the important early events in tumour initiation would potentially prevent the tumours using chemoprevention strategies. The CTF felt that there are many virology, proteomics and inflammation experts in Singapore, thus the potential for Singapore to contribute to this research area.

36. New treatment approach to treat metastatic and/or resistant cancer – to understand the mechanistic underpinnings of resistance & metastases so as to identify targets and pathways for enhancing drug pipeline development & therapeutic strategies. This is a key area of cancer research. Relevant capabilities and talents are available to develop this further such that it could encompass Singapore's strengths in omics, molecular biology (discovery, and mechanistic studies) and early phase clinical trials (potential interventions).

37. Cancer Immunotherapy – to inform patient selection, maximise effects, and improve survival and outcome of cancer. This area encompasses two broad therapeutic areas: Antibody-based and Cellular Immunotherapy. It is related to the tumour microenvironment (Para 34) as the immune cells and their functions form part of the microenvironment. Why selection of targets may relate to unique proteins expressed on the surface of tumour cells, the understanding of the tumour microenvironment and how it impact on the host immune system will determine response and resistance to immunotherapy. How these factors can be modulated to augment immune response will be potential strategy to enhance immunotherapy and overcome drug resistance. The field has been propelled by multiple FDA approvals for immune oncology drugs within a short span of a few years, transforming and redefining the treatment of very difficult cancers such as malignant melanoma. In refractory incurable leukaemia and some lymphomas, some stunning results with complete remissions have raised optimism for immunotherapy against previously hopeless cancers. Most big pharmaceutical companies have also made immune oncology and immunotherapy their major priority.

38. The CTF is of the view that Singapore has a growing human capability and expertise, and A*STAR has built a number of relevant facilities and infrastructure over the last few years. The recent establishment of the Experimental Biologics Centre (EBC) will further help to enhance delivery of these treatments to the clinic. There are excellent cancer centres with outstanding clinical trial units to conduct the clinical testing, and internationally accredited transplant programmes and good manufacturing practice (GMP) level tissue engineering facilities to produce the cellular products. In addition, there is significant interest from basic scientists in immunology in this area of work and unique spectrum of cancers that are more prevalent in Asia.

39. Treatment and adherence – To minimise variation in cancer care and to improve adherence to medication. Treatment adherence is crucial to obtain optimal outcomes such as cure or improvement in quality-of-life. This is especially important in older adults that tend to have multiple co-morbidities and cognitive and sensory impairments that could affect treatment adherence. Studies have shown that adherence rate for oral anticancer drugs could be as low as 16% and as high as 100%. It is also expected that non-adherence rate in cancer patients will be increasing in the coming years with the rise in chronic health conditions,

increased long-term maintenance therapy, as well as growth in the use of oral anticancer drugs.

40. Palliative care – To develop better strategies around care, financing, and pain and symptoms relief. Incurable cancer becomes a terminal disease requiring best palliative care and community infrastructure and manpower support. When it comes to advanced cancer, many cancer patients spend their last months of life in significant pain, in and out of the hospital, and do not die in their preferred location. Singapore is renowned for teaching palliative care to our regional neighbours. While there is a foundation for palliative care in Singapore, and Singapore is recognised for teaching palliative care to our regional neighbours, this area is not as developed as compared to many other countries. As the cancer burden in Singapore is high and rising, it is a key imperative to improve this.

(II) GAPS/ROADBLOCKS AND RECOMMENDATIONS

41. The CTF has identified several gaps that may impede cancer research in Singapore. Many are not unique to the cancer field and will likely need a more holistic approach in tackling the issues.

42. Collaboration versus competition. While there is a general willingness from the cancer research community to work together, it has been difficult to establish true, open collaborations due to, in part, the need to compete for the same funding across the different institutions. This is exacerbated by the fact that there are more cancer researchers in Singapore than any other disease areas, but similar funding quantum was allocated to all priority disease areas. Moreover, the current funding policies only allow for a single lead researcher/institution for each programme/ grant even though the collaborating researchers/institutions could have significant contribution to the programme/grant.

43. Personal data protection act (PDPA) and human biomedical research act (HBRA). The PDPA came into full enactment in Jul 2014, and the new HBRA, which rode on the PDPA, was passed in August 2015. The CTF has concerns that some hospitals may not be aware of the full implications of the PDPA, and could therefore be running afoul of the regulations. The research community is also facing issues on the implementation of the HBRA, as most researchers previously did not seek consent for the use of participants' personal data. There is also another layer of problem as there is no system in place to deal with the use of legacy and archival data which had not sought earlier consent. As a result, there has been a disruptive shutdown of numerous databases due to perceived violations, and researchers are not being able to mine data from hospital records.

44. Accessibility of equipment/platforms. As there are multiple dedicated cancer research institutes in Singapore, there is a tendency for each institution to develop its own capabilities, including procuring advanced, high-end equipment. The CTF felt that it was necessary for greater sharing of these equipment/platforms, so as to reduce wastage and avoid duplication.

45. Lack of patient information-linked biobank samples. The CTF felt that it was essential to build a suitable national framework to collect tissues samples that were appropriate for the different types of analysis needed. For instance, the standards of tissues required for immunology assays are different from those required for genomic sequencing. In addition, these samples are only informative for research if they are linked to the patient phenotypic data.

46. Lack of national programmes for cancer data integration (e.g. tracking of outcomes etc.). This is related to the roadblock "collaboration versus competition". The current cancer research is driven based on the interest of individual investigators and institutions. Certain types of research activities (e.g. conduct of clinical trials) and platforms (e.g. tumour sequencing and immune-phenotyping) may be broadly applicable to multiple cancer types. There is no national programmes or national level office for cancer research with dedicated funding which are present for other disease groups such as diabetes and infectious diseases. There is a need for constant engagement and coordination of the research activities for collaborations among basic scientists, clinician-scientists and relevant government agencies (e.g. HPB, ACE), and also to collect, track and integrate the research outcomes from different institutions in Singapore, to translate them to clinical practice and economic potentials.

47. Short-termism. Drug development from drug discovery to commercialisation is a long process, with high rates of attrition – only about 5% of drugs reaching phase I clinical trials are eventually registered. The key to bridging this biotechnology "valley of death" is to have highly collaborative, scientific research aimed at thorough understanding of the biological target and development of biomarkers to support early phase clinical trials. This potential exists in Singapore, where the whole range of research expertise needed is available in close proximity with each other. In reality, a viable goal for drug development in Singapore should be to aim to reach proof of concept. Even attrition of drugs will lead to enhanced knowledge that reduces the risk of failure of the next product.

48. Gap between discovery research, clinical research and commercialisation. Unlike the Silicon Valley in the US, there is a lack of commercial expertise and venture capitalists in Singapore. This is a huge gap in the later stage of the drug development process, and the question remains how Singapore can bring in industry players early. On a related note, although there are funding available for discovery research, the CTF felt that there is still a gap for the translation of discovery research to clinical trials. There is a critical missing piece of biotechnology incubators that generate data needed to support the clinical trials and this entity is best placed outside of academic institutions as their performance should be judged differently.

49. Training of Clinician Scientists. An important factor for the growth and success of cancer research in Singapore over the years is the constant stream of

clinician-scientists that the specialty can attract and train. Clinician-scientists are critical in effective translation and act as an important bridge between discovery science and implementation science. Cancer is a fast moving field that is highly linked to advances in understanding of molecular biology and genetics. This means that Singapore will constantly need to re-invent and train clinician-scientists in new areas, and with different expertise needs to be constantly produced e.g. current lack in areas such as bioinformatics, and cellular and immunotherapy, next generation genomics, RNA biology, and synthetic biology. The CTF feels that this is currently under threat as training pipeline and manpower planning for haematology and oncology are based on clinical needs, without taking into account the important aspect of research.

Recommendations to Address the Gaps/Roadblocks

50. To address these roadblocks and gaps, the CTF suggests the following recommendations:

51. Recommendation 1: Provide levers and incentives for researchers to work together; some key performance indicators (KPIs) could be team based.

52. Recommendation 2: Regulatory team to engage the different institutions to address the impact of PDPA and HBRA on cancer research.

53. Recommendation 3: Consolidate key national infrastructure and equipment to facilitate sharing and collaborations, and develop principles for the harmonisation, access, and storage of tissue samples and data.

(a) For accessibility, one of the good motions that has occurred is the creation of adjunct appointments for clinician scientists at scientific institutions such as A*STAR. The CTF recommends that scientists should also be given opportunities to have adjunct positions at academic health centres close to the translational and clinical interface.
(b) For the longer term planning for high-cost equipment, the CTF recommends centralising such equipment (e.g. proteomics and genomics equipment).
(c) For patient information-linked biobank samples, the CTF recommends that the relevant institutions should have proper engagement and open discussion with the underlying principle of benefiting all researchers; Singapore could focus on the two main tissue repositories housed in the two AMCs, with funding to support and expand these biobanks; harmonisation of data fields and protocols; and a scientific committee represented by the key stakeholders to evaluate merits of proposals that want to utilise the samples.

54. Recommendation 4: Ensure that funding for cancer research takes a longer-term perspective, and create platforms to train clinician scientists and develop innovation and commercialisation skills.

(a) There should be better recognition that some things take time to build, and Singapore should be building for the long term. This is particularly important for national resources and research programmes.
(b) There should be more clinician-scientists for bridging the discoveries from basic, translational to clinical delivery, with consideration of the constantly changing new areas of expertise in research other than for clinical needs. The CTF feels that at least 20-25% of haematologists / oncologists should be clinician-scientists. There should also be creation of more platforms for bilateral engagement between basic scientists and clinician-scientists.
(c) In terms of commercialisation, the CTF recommends a platform to engage and educate the researchers so that the culture can change from one purely of academic research to one of innovation and commercialisation. One good way to start would be roadshows and an annual workshop for educating and reviewing potential commercialisation projects.

55. Recommendation 5: Set up national programmes for cancer data integration.

(a) Collaborations should occur where suitable and possible, while also allowing space for individual investigators' science to blossom.
(b) The clinical data for the different cancer types in institutions should be harmonised and merged, i.e. unified colon, lung and breast cancer databases in Singapore. The databases should be populated with patient data, pathology records, treatment and follow-up information.
(c) A professional membership body of cancer researchers in Singapore should be established, similar to the American Association for Cancer Research (AACR) in the US and Japan Cancer Association (JCA) in Japan. At present, there is no regular forum for cancer researchers in Singapore to present their research and exchange ideas.

56. Recommendation 6: To link up with Precision Medicine Steering Committee (PMSC) on potential synergies; to ensure maximum information, genomic data from cancer patients (germline or tumour-sequencing) be generated in facilities that have reputations for good quality data, are cost effective, and the data should be processed in a manner that allows future integration with other data sets and clinical information.

I. CONCLUSION

57. In summary, cancer is a highly prevalent disease around the world, including in Asia and Singapore. The public sector's research investments have

led to the development of basic, translational and clinical cancer research capabilities in Singapore, which have yielded various achievements in terms of scientific, health and economic outcomes. The CTF recommends three priority themes for the HBMS OF-LCG, as well as 10 broad focus areas and six recommendations under the five-year research roadmap.

Annex – Composition of the Cancer Taskforce

S/N	Name	Designation
1	Prof Chng Wee Joo *(Co-Chair)*	Director, National University Cancer Institute, Singapore (NCIS) Head & Senior Consultant, Division of Haematology, Department of Haematology-Oncology, NCIS Leader, Haematologic Malignancy Tumour Group, NCIS Professor, Yong Loo Lin School of Medicine (YLLSoM), National University of Singapore (NUS) Deputy Director, Cancer Science Institute of Singapore (CSI), NUS
2	Prof Patrick Casey *(Co-Chair)*	Senior Vice Dean (Research), Duke-NUS Medical School (Duke-NUS) Professor, Cancer & Stem Cell Biology Programme, Duke-NUS
3	Prof Eric Finkelstein	Director, Lien Centre for Palliative Care, Duke-NUS Professor, Health Services and Systems Research Programme, Duke-NUS
4	Adjunct Prof Goh Boon Cher	Deputy Director, CSI, NUS Programme Leader and Senior Principal Investigator, CSI, NUS Head and Senior Consultant, Department of Haematology-Oncology, NCIS Director, Investigational Medicine Unit, National University Health System (NUHS)
5	Prof Russell Gruen	Vice Dean (Research), Lee Kong Chian School of Medicine (LKCSoM), Nanyang Technological University (NTU) Professor of Surgery, LKCSoM, NTU Director, Nanyang Institute of Technology in Health and Medicine, NTU
6	Prof Hong Wanjin	Executive Director, Institute of Molecular and Cell Biology (IMCB), A*STAR Honorary Joint Professor, Department of Biochemistry, YLLSoM, NUS
7	Dr Mark McHale	Chief Operating Officer, Chief Scientific Officer and Founder, ASLAN Pharmaceuticals
8	Prof Patrick Tan	Deputy Executive Director, Biomedical Research Council (BMRC), A*STAR Professor, Cancer and Stem Cell Biology Programme, Duke-NUS Director, Genome Biology Facility, Duke-NUS Associate Director (Genomic Medicine), Genome Institute of Singapore (GIS), A*STAR

		Senior Group Leader, GIS, A*STAR Senior Principal Investigator, CSI, NUS
9	A/Prof Tan Soo Yong	Head, Department of Pathology, National University Hospital Head, Histopathology and Advanced Molecular Pathology Laboratory, A*STAR Senior Principal Investigator, IMCB, A*STAR
10	A/Prof Teo Yik Ying	Vice Dean (Research), Saw Swee Hock School of Public Health (SSPH), NUS Domain Leader, Biostatistics Domain, SSPH, NUS Director, Centre for Infectious Disease Epidemiology and Research, NUHS Director, Centre for Health Services and Policy Research, NUHS
11	A/Prof Toh Han Chong	Deputy Director, National Cancer Centre Singapore (NCCS), Singapore Health Services (SingHealth) Senior Consultant, Department of Medical Oncology, NCCS, SingHealth Director, Cryopreservation laboratory, Department of Medical Oncology, NCCS, SingHealth Chairman, Cell Tissue- Based Therapy Committee, NCCS, SingHealth Associate Professor, Cancer and Stem Cell Biology Program, Duke-NUS
12	A/Prof Narayanan Gopalakrishna Iyer	Senior Consultant, NCCS, Singhealth