REVIEW

Research on cancer diagnosis in Malaysia: current status

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Abstract

Cancer is a major morbidity and mortality concern in Malaysia. Based on National Cancer Registry data, the Malaysian population is estimated to bear a cancer burden of about 40,000 new cases per year, and a cumulative lifetime risk of about 1:4. Cancer research in Malaysia has to consider needs relevant to our population, and resources constraints.   Hence, funding bodies prioritise cancers of high prevalence, unique to our community and posing specific clinical problems. Cancer diagnosis is crucial to cancer management. While cancer diagnosis research largely aims at improvements in diagnostic information towards more appropriate therapy, it also impacts upon policy development and other areas of cancer management. The scope of cancer diagnosis upon which this paper is based, and their possible impact on other R&D areas, has been broadly categorized into: (1) identification of aetiological agents and their linkages to the development of precancer and cancer (impact on policy development, cancer prevention and treatment), (2) cancer biology and pathogenesis (impact on cancer prevention, treatment strategies and product development), (3) improvements in accuracy, sensitivity and specificity in cancer detection, monitoring and classification (impact on technology development) and (4) prognostic and predictive parameters (impact on treatment strategies). This paper is based on data collected by the Working Group on Cancer Diagnosis Research for the First National Conference on Cancer Research Coordination in April 2004. Data was collated from the databases of Institutions/Universities where the authors are employed, the Ministry of Science, Technology and Innovation (MOSTI) and targeted survey feedback from key cancer researchers. Under the 7th Malaysia Plan, 76 cancer projects were funded through the Intensified Research in Priority Areas (IRPA) scheme of MOSTI, amounting to almost RM15 million of grant money. 47(61.8%) of these projects were substantially in cancer diagnosis, accounting for 65.6% (RM 9.7 million) of cancer project funds. The 8th Malaysia Plan saw a change in research strategy. The IRPA agency fielded several top-down projects which encouraged a multicentre and multidisciplinary approach.   This resulted in larger funding per project i.e. RM32 million for 49 projects. There was also a surge of interest in drug development and natural products. Because of this shift in direction, cancer diagnosis projects constituted only 51% of IRPA-funded cancer projects.   Nonetheless funding for cancer diagnosis research has exceeded that of the 7th Malaysia Plan, being RM12.5 million by March 2004. The majority of such research is carried out at the Universities, engaging

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a large number of young scientists and postgraduate students (51 MSc and 21 PhD). A lot of research findings presented at scientific meetings have not yet been published and there is a glaring shortage of patents and commercialization of research findings (such as creation of test kits). Because diagnosis is very much a part of clinical practice, many researchers felt satisfied and confident that their work will be translated into practice and will significantly improve diagnostic services in Malaysia. National guidelines and consensus development on at least three malignancies i.e. breast cancer, oral cancer and lymphoma, have substantial basis in local R&D work. Problems encountered in research included (1) insufficient funding to realize research objectives, (2) lack of local expertise (most research assistants are inexperienced BSc graduates with no or minimal research experience), (3) inadequate technical support from vendors during equipment failure, (4) inexperienced Institutional development units to assist in product development, (5) lack of venture capital for commercialization of findings, and (6) inadequate incentives to undertake research. Researchers pointed out that plans to promote research should include the establishment of (1) regional and national cancer tissue banks, (2) a National Cancer Research Institute, (3) a dedicated cancer research fund, (4) a registry of cancer researchers, (5) national research coordinators, (6) improved coverage by the National Cancer Registry, (7) more international collaboration, (8) a better career structure for researchers, (9) improved Institutional support for product realization, and (10) better recognition for cancer researchers.

Key words: cancer diagnosis, research and development, cancer prevalence, research funding.

INTRODUCTION

Cancer has emerged as a major cause of morbidity and mortality in Malaysia. The increasing prevalence of neoplastic diseases in Malaysia has been highlighted in the first report of the National Cancer Registry.[1] Based on Registry data, it has been estimated that the Malaysian population bears a cancer burden of about 40,000 new cancer cases per year, and a cumulative lifetime risk of about 1:4.[2] This translates to a substantial loss of productive human resource and a major drain on the healthcare budget, as each cancer patient draws a complex and expensive web of laboratory investigations, therapeutic measures and socio-economic support.

The battle against cancer is an essential and multi-faceted one. While it is important that we should continually hone our clinical skills and master our investigative and therapeutic tools, the battle will be lost if there is no search for new knowledge of the "enemy" and development of new strategies to counter it. In the research effort, it is important to bear in mind the needs relevant to our local population, and the constraints of limited resources. Hence, funding bodies tend to support research into cancers (1) of high prevalence, (2) unique to our community and (3) posing specific clinical problems. In the Malaysian context, cancers of high prevalence are, by rank order, malignancies of the lung, nasopharynx, large intestine, lympho-haemopoietic system, genital tract and liver. Nasopharyngeal carcinoma is the second most

common cancer in males (8%), after lung cancer. It is noteworthy that the age-standardised incidence rate (ASR) for Malaysian Chinese men (23.3) is the second highest in the World, being just behind that of Hong Kong (24.3). Prostate cancer ranks 6th in male cancers and is expected to increase in importance as the population ages. In adult females, breast cancer has emerged as the most common malignancy, accounting for 30.4% of all female cancers with a cumulative lifetime risk of 1 in 19. Cervical cancer ranks a close second (12% of cancers in females). In view of our relatively young population, childhood leukaemias and solid cancers also require special focus. Our multiracial population also draws attention to cancers unique to certain ethnic groups such as oral cancer, while also providing an opportunity to study genetic polymorphisms and their linkages to neoplastic disease. Reports that only about 16% of cancers are detected in Stage I or Stage II,[3] and that 82% of gastric cancer present with Stage IV disease[4] have drawn attention to the late detection of cancer as an important negative factor in the Malaysian setting.

THE SCOPE OF CANCER DIAGNOSIS RESEARCH

The diagnosis of cancer is one of the most important steps in the management of cancer. While it is well appreciated that an inaccurate or substandard diagnosis would lead to wrong or delayed treatment and perhaps even the loss of life, it is noteworthy that the diagnosis of cancer

is not merely the detection of the presence of a malignancy. In line with advancements in therapeutic options, there is increasing demand for more information on the nature and characteristic of each and every cancer detected. For example, today, the diagnostic histopathologist hardly ever reports on a breast cancer as a simple diagnostic phrase, but is also expected to assess for a range of prognostic and predictive indicators such as tumour size, cancer type, histological grade, oestrogen/ progesterone receptor status, c-erbB-2 oncogene expression status, the presence of lymphovascular invasion, surgical margin clearance, lymph node status, etc. While research in cancer diagnosis is largely aimed at improvements in diagnostic information towards more appropriate choice of therapy for the cancer patient, cancer diagnosis research will also impact upon policy development and many other areas of cancer management. The scope of cancer diagnosis upon which this paper is based, and their possible impact on other R&D areas, has been broadly categorized into:

1. Identification of aetiological agents and their linkages to the development of precancer and cancer (impact on policy development, cancer prevention and treatment)
2. Cancer biology and pathogenesis (impact on cancer prevention, treatment strategies and product development)
3. Improvements in accuracy, sensitivity and specificity in cancer detection, monitoring and classification (impact on technology development)
4. Prognostic and predictive parameters (impact on treatment strategies)

Data collection, limitations and omissions

This paper presents the results of data collected by the Working Group on Cancer Diagnosis Research (the authors) for the First National Conference on Cancer Research Coordination in April 2004. Data was collated from the databases of the various Institutions/Universities where the authors are employed, the Ministry of Science, Technology and Innovation (MOSTI) and targeted survey feedback from key cancer researchers. From the outset, variation in the perception of what constitutes cancer "diagnosis" among researchers would have affected the response to the call for information. As clarified earlier, there would be considerable overlap with projects on cancer epidemiology, prevention and treatment, etc. More importantly, due to the short time available for the preparation of this

paper and severe personnel constraints, a comprehensive survey of cancer researchers could not be conducted. Notably, some Institutions have not been included in the targeted database collection, in particular, the International Islamic University, Universities without medical schools, biotechnology institutions, MINT, FRIM, SIRIM, the Malaysian Palm Oil Board, all private Universities, all private hospitals, and many hospitals of the Ministry of Health. In this paper, more emphasis has been given to information listed in the official database of the IRPA monitoring unit of MOSTI, which understandably will not carry details of research activities and findings. Description of the findings described here would thus be somewhat skewed towards those within the personal knowledge of the authors. We acknowledge unreservedly that this does not capture the whole picture of cancer diagnosis research in Malaysia. Notwithstanding these limitations, we believe that valuable insights have been gained from this exercise, which can assist in the deliberations of this Conference.

STAKEHOLDERS & FUNDING AGENCIES

In a broad sense, the largest stakeholder in cancer research is the public, who represents the patient seeking relief from the affliction of cancer, whether in the present or future. It is not surprising then that the cancer research effort is spread widely over numerous public and private medical institutions with direct patient contact (Table 1).

The introduction of IRPA funding since the 5th Malaysia Plan has seen a quantum leap in cancer research in the public institutions. Through the IRPA and National Biotechnology Directorate schemes, MOSTI is notably one of the largest granting agencies for research into cancer diagnosis today (Table 2). More recently, the public has also directly supported cancer research through donations to the National Cancer Council (MAKNA) and Cancer Research Initiatives Foundation (CARIF). Universities with Medical Schools also traditionally fund short-term cancer research projects among academic staff and postgraduate students (Table 3). We would like to point out that there are numerous other research activities related to cancer diagnosis that are not officially funded, carried out in the Universities and the Ministry of Health, which are not included into this enumeration. These include research activities carried out in the course of medical specialist

Table 1: Institutions involved in Cancer Research in Malaysia

Public	Private
• Ministry of Health (Hospitals, Institutions, CRC, IMR) • Universities • Malaysian Palm Oil Board • MINT • FRIM • Others	• National Cancer Council (MAKNA) • Cancer Research Initiatives Foundation (CARIF) • Private Hospitals • Nilai Cancer Institute • Others

Table 2: Funding for Cancer Diagnosis Research Projects in Malaysia

	7th Malaysia Plan		8th Malaysia Plan (till March 2004)	
	No. project	Funding RM	No. project	Funding RM
IRPA	47*	9,731,893	25*	12,520,695
FRGS	-	-	5	423,961
Internal funds (Universities)	-	-	71	642,696
MAKNA	-	-	6	619,114
CARIF	-	-	4	2,000,000
	47	**9,731,893**	**111**	**16,206,466**

* Includes National Biotechnology Directorate Projects

Table 3: Internally-funded University research projects on cancer diagnosis (2000-2003)

University	No. Projects	Funding (RM)
UM	39	278,772
UKM	13	58,168
USM	11	190,275
UPM	5	50,000
UNIMAS	3	65,481
TOTAL	**71**	**642,696**

(Clinical Masters Programmes) and allied health science training. Furthermore, projects funded from abroad have not been enumerated.

RESEARCH PRIORITIES

Under the 7th Malaysia Plan, 76 cancer projects were funded through IRPA, amounting to almost RM15 million of grant money (Table 4). 47(61.8%) of these projects were substantially in the field of cancer diagnosis, and carried 65.6% (RM 9.7 million) of the funds for cancer projects. Projects supported by National Biotechnology Directorate grants gained a significant advantage in the rapid absorption of genomic and proteomic biotechnology into the cancer research armamentarium.

The 8th Malaysia Plan saw a change in research strategy. The IRPA agency fielded several top-down projects (PR and SR) which encouraged a

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multicentre and multidisciplinary research approach. This was characterized by larger funding per project compared to the 7th Malaysia Plan i.e. RM32 million for 49 projects (Table 4). There was also a surge of interest in drug development and natural products. In cancer research, this was reflected in a large number of projects investigating anticancer properties of local plants, particularly at basic science or pre-clinical University departments. University Putra Malaysia appears to have the largest number of such projects. Because of this shift in direction, cancer diagnosis projects constituted only 51% of all IRPA-funded cancer projects. Nonetheless the amount of funding released for cancer diagnosis research has exceeded that of the 7th Malaysia Plan, being RM12.5 million by the middle of the 8th Malaysia Plan.

ENABLING TECHNOLOGIES

It is recognized that the development and progression of cancer is a multi-step process involving numerous cellular events. These events have to bring about changes at the genetic level for the changes to be transmissible to descendents of the transformed cell. Hence cancer research has shifted from a purely morphological level to the molecular and genomic level. Current research tends to focus on (1) abnormalities in the regulation of cell growth and cell death, particularly the overexpression of oncogenes, inactivation of tumour suppressor genes and involvement of the apoptosis regulating genes, (2) the mechanisms whereby tumour cells overcome the biological clock (Hayflick limit) to achieve a state of "immortalization", (3) the acquisition of abnormal cellular behaviour which allow cancer cells to invade tissues and metastasize to other parts of the body, and (4) the events of tumour progression and heterogeneity characterized by the emergence of cancer subclones with greater metastatic potential and resistance to treatment. It is increasingly obvious that these events do not occur in a serial manner nor in isolation of each other. Hence unravelling the biology of cancer will require investigations of interactions between molecular events, at gene and protein levels, and at the levels of their expressions and polymorphisms. In the light of this, traditional research methods which assess one event at a time have been viewed as too labour-intensive and time-consuming. With the advent of genomic pathology, cancer researchers have been quick to cash in on the emergence of new enabling technologies, particularly (1) proteomic and genomic technologies, (2) microarrays, such as at tissue, cDNA, oligonucleotide and peptic nucleic acid levels, and (3) computational biology and bioinformatics, to provide robotics, image processing, data storage and retrieval, database design and data analysis to bring about quantitative rather than qualitative assessments.

It is not surprising that a review of current IRPA-funded cancer diagnosis projects showed that 73% of projects utilize proteomic and genomic technologies to investigate events at molecular and cellular levels. The emergence of Biotechnology Institutes (Table 5) has also provided an impetus towards collaboration between medical science and biotechnology in cancer diagnosis research.

RESEARCH QUESTIONS

Table 6 shows the distribution of recent and current IRPA-funded cancer diagnosis research projects according to broad focus areas.

AETIOLOGICAL AGENTS AND CAUSATION OF CANCER

It has long been known that certain viral agents have aetiological linkages to cancer. Earlier seminal studies have established the causative association between the hepatitis B virus (HBV) and liver cancer[5] and between the Epstein-Barr virus (EBV) and nasopharyngeal carcinoma (NPC) in Malaysians.[6]

Past investigations have contributed largely to the knowledge of EBV serology, in particular, the use of the viral capsid antigen (VCA) as a marker of tumour load.[7] More recent studies aimed at characterizing the viral latent membrane protein 1 (LMP-1), immunomapping of antigenic epitopes and molecular typing of NPC-associated EBV. Studies indicate a high prevalence of EBV in Asia with viral isolates having typical characteristics of the putative viral oncogene, LMP-1, such as the loss of the Xho 1 restriction site in Exon 1 and the 30-bp deletion in Exon 3. A recent finding that 16% of NPC biopsies possessed both the deleted and the undeleted variants has raised the notion of dual infection. A discrepancy in the frequency of the 30-bp deletion between throat washings (20%) and postnasal space biopsies (100%) in NPC patients suggests that this deletion is specific for viral isolates from primary tumour sites.[8]

On-going studies on Hodgkin's disease and malignant lymphomas have also revealed a high frequency of association with the Epstein-Barr

Table 4: IRPA-Funded Cancer Diagnosis Projects by Institution (7th & 8th Malaysia Plan)

	7th Malaysia Plan				8th Malaysia Plan (Till March 2004)			
	Cancer		*Cancer Diagnosis*		*Cancer*		*Cancer diagnosis*	
Principal investigation	No.	Funding RM	No.	Funding RM	No.	Funding RM	No.	Funding RM
IMR	14	1,889,055	11	1,531,388	3	3,855,675	2	3,165,675**
UKM	16	3,158,795	11	2,315,460	9	2,691,940	6	1,628,940
UPM	8	1,757,380	3	845,800	19	16,303,840	3	506,500
USM	10	1,924,480	3	539,500	8	3,061,851	4	1,509,920
UM	23	5,516,745	17	4,163,745*	7	4,191,660	7	4,191,660
MPOB	1	40,000	0				0	
MINT	3	475,000	2	336,000			0	
FRIM	1	75,000	0				0	
UTP					1	271,000	1	271,000
UNIMAS					2	1,247,000	2	1,247,000
TOTAL	**76**	**14,836,455**	**47(61.8%)**	**9,731,893 (65.6%)**	**49**	**31,622,966**	**25 (51%)**	**12,520,695 (39.6%)**

*Includes 1 Nat Biotech Directorate project (RM1,972,000)
** Includes 1 Nat Biotech Directorate project (RM2,543,675)

Table 5: Biotechnology Research in Public Universities, Malaysia

- Institute of BioSciences, UM
- Malaysian Proteomic Analysis Facility, Biotechnology Centre, UM
- UKM Molecular Biology Institute (UMBI)
- Center for Gene Analysis & Technology, UKM
- Institute of Biosciences, UPM
- Human Genome Institute, USM
- Institute of Molecular Virology & Public Health, UNIMAS
- Institute of Biotechnolgy, UiTM

Table 6: Research Focus of IRPA-funded Cancer Diagnosis Projects (7th and 8th Malaysia Plans)

Research question	Number (%)
Aetiological agents and causation of cancer	15 (20.8)
Cancer biology	27 (37.5)
Detection and Monitoring	12 (16.7)
Prognostic and predictive characteristics	18 (25.0)
Total	**72 (100)**

virus and 30-bp deletion in the LMP-1 gene.[9,10] The association was noted to be more prevalent in B-cell (23%) than T-cell (12%) lymphomas.[11]

In the field of liver cancer, an on-going IRPA-funded PR project investigates the characterization of virological markers associated with hepatocellular carcinoma in patients chronically infected with Hepatitis B virus and/ or Hepatitis C virus.

Studies have also strengthened evidence for the aetiological role of the human papilloma virus in cancer of the cervix, and helped to elucidate its interaction with the p53 and Bcl-2 genes.[12,13] The role of other infective agents in cervical cancer continue to be investigated. A study on microsatellite instability status, molecular and histopathological phenotypes of Helicobacter pylori-associated gastric carcinoma is of note.

Several studies also target the hereditary basis of cancers. There is considerable interest in mutations of the BRCA-1 and BRCA-2 genes in breast and ovarian cancers.[14,15] Mutational studies in familial adenomatous polyposis (FAP) have led to the detection of an Arg283Ter mutation in the APC gene in a Chinese family.[16]

CANCER BIOLOGY (PATHOLOGY, PATHOGENESIS AND PATHOPHYSIOLOGY OF CANCER)

Earlier studies on the prevalence and patterns of the various types of cancers have provided important groundwork data for current investigations.[17-22] Under the 7th and 8th Malaysian Plans, a majority of cancer diagnosis studies have shifted from such baseline studies and have instead focused on unravelling the complex cellular mechanisms of malignant transformation and cancer cell behaviour. Furthermore, with the advent of molecular biotechnology and computational bioinformatics, researchers now use a combination of technologies (such as immunocytochemistry, imaging, proteomic and genomic technologies) in their investigations. Almost all common cancers in Malaysia have been targeted. Most of the studies investigate abnormal protein expressions (cytokines, chemokines, glycoproteins, etc) by cancer cells, and/or demonstrate chromosomal alterations, rearrangements, deletions and mutations in candidate genes. Some examples of recent findings are listed below:
- ret/PTC mutations in papillary carcinoma of the thyroid[23,24]

- p53 mutations in renal tumours[25]
- p53 in cervical carcinogenesis[26]
- Regulation of proliferation and apoptosis in lymphoma[27]
- Beta-catenin in hepatocellular carcinoma[28]
- Cytokine expressions in lymphoma[29]
- Coduplication of MLL and FLT3 genes in acute myeloid leukaemia[30]
- Retinoblastoma (rb1) gene rearrangements in acute myeloid leukaemia[31]
- Expression of p16 proteins in acute myeloid leukaemia[32]

The demonstration of chromosomal rearrangements, cytogenetic aberrations and gene duplications in human cancer cells by various Malaysian researchers have underscored the widespread genetic basis of neoplastic transformation.[30,33-35] Several multicentre studies have now embarked on the molecular profiling of carcinoma of the nasopharynx, breast, and oral mucosa. Other ongoing studies listed below (not exhaustive), give an indication of the diverse attempts being made in understanding cancer pathogenesis and pathophysiology:
- Apoptosis and tumour necrosis factor in neoplasia
- Interleukin receptors in tumorogenesis
- Characterization of genes involved in the regulation of p53
- Glycoprotein expression in breast, endometrial and ovarian cancers
- Cell-cycle regulators in hepatocellular carcinoma
- p53 and apoptosis gene mutations in hepatocellular carcinoma
- E-Cadherin expression in breast carcinoma
- Loss of heterozygosity of the Wilms tumour suppressor gene in breast cancer
- Quantification of Her2 gene in breast cancer using real-time Q-PCR
- Expression of GP200 MR6 antigen in breast cancer
- Mutations of BRCA1 and BRCA2 genes in breast cancer
- Gene expression in NPC using SAGE and microarray
- Chromosome fragility in NPC
- Chromosomal alterations in malignant lymphoma
- CD56 in acute myeloid leukaemia
- Perchoric-acid soluble protein in acute leukaemia
- Detection of brc-abl gene mutations in leukaemia using multiplex RT-PCR
- Alterations in cytokines and apoptotic

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pathways in acute myeloid leukaemia
- t(8:21) in acute myeloid leukaemia
- p53, Ki-67 & Bcl-2 expression in oral squamous cell carcinoma
- Molecular mapping of prostate cancer signaling networks using proteomic approach
- Androgen receptor gene and prostate cancer
- p53 and p21/WAF-1 expression in prostate cancer
- Effect of tumour necrosis factor on MHC1 gene expression in HPV transformed cells
- Retinoblastoma gene products in cervical cancer and precancer
- PPAR ligands in ovarian and cervical cancers
- Ctcf/Yb-1 transcription factors in cervical cancer
- Alterations in expression of oncogenes and tumour suppressor genes in gynaecological cancers
- Detection and characterization of PAX8-PPAR gene in thyroid neoplasms
- H-ras mutations in thyroid carcinoma
- P53 expression and gene mutations in childhood rhabdomyosarcoma
- IGF-1R in osteosarcoma
- Cytogenetic studies on retinoblastomas
- Loss of heterozygosity and molecular studies on gliomas
- p53 in lung cancer
- Functional analysis of novel lung carcinoma genes using RNA inference and microarrays
- Identification of differentially regulated genes in lung carcinoma

Of note are studies which have drawn upon both biological and physical sciences to unravel events in cancer tissues. An example is a neutron activation analysis to investigate the microenvironment of human breast tissue within which microcalcifications develop. Among other findings, this PhD work has shown a significant correlation for Rb and Zn in breast cancer tissues.[36,37] Current work on image analysis of cancers may also reveal novel findings.[38]

Although many of these studies, being of a fundamental nature, have yet to be translated into clinical use, these have served to increase knowledge in the understanding of cancer cell biology. In additional, the findings have the potential of being utilized for more accurate diagnosis of cancer and may also provide tangible targets for anticancer therapy.[39-41] A current study into dendritic cells and vaccine development in breast cancers, leukaemias and lymphomas is worthy of note.

CANCER DETECTION, MONITORING AND CLASSIFICATION

Studies into enhancement of diagnostic capability for the detection, monitoring and classification of cancer have more direct clinical bearing. A few examples of such potential translations from the bench to the bed are related below:
- A multicentre study of CD44 expression by childhood neuroblastic tumours showed that CD44 expression correlated with the International Neuroblastoma Pathology Classification. Furthermore, expression of CD44 correlated with favouable histology and may be useful as a marker in the staging of the disease.[42]
- In a study of 20 healthy volunteers, 22 monocytic AML (M4 and M5) and 20 acute lymphoblastic leukaemia (ALL), EMA monoclonal antibody was demonstrated to show a strong association (P<0.001) with all the other known markers (CD11c, CD14 and intracellular CD68) of monocytic-macrophage lineage in acute leukaemia subtypes. EMA also showed 100% specificity and 81.8% sensitivity in the diagnosis of AML M4 and M5. It was concluded that monoclonal antibody EMA (clone E29) is a useful marker in the classification of acute myeloid leukaemia and can be used as a supplementary analysis for the diagnosis of acute leukemia with monocytic involvement.[39]
- Discriminate analysis of six trace element concentrations measured by instrumental neutron activation analysis in 26 paired-samples of malignant and histologically normal human breast tissues show that the elements of Ca, Rb and BR provided correct classification for 24 out of 26 normal samples and 22 out of 26 malignant samples.[43] Further PhD work from this group now looks into analysis of breast composition using radiographic techniques which may have utility in improving the accuracy of mammographic detection of breast cancer.[44]

No less important, although not recounted here in detail, are studies into improvements in fine needle aspiration cytological diagnosis of childhood tumours, NPC, breast cancer[45,46] and lymphomas, accuracy of mammotomy in the diagnosis of breast cancer, early detection of minimal and residual leukaemia, detection of bcr-abl fusion gene in acute leukaemia by PCR, molecular and flow cytometric tests for diagnosis and prognosis of leukaemia and lymphomas, and the application of helical CT, MRI, electrical

impedence with TransScan TS2000 and other radiological techniques towards improved cancer detection/monitoring.[47] Many of these studies may have commercial potential, such as studies on the optimization and setting up of immunoassays for alfa feto protein (AFP) using locally generated antibodies, affinity purification of Lectin C from Champedak (*Artocarpus integer*) to locate potential markers in nasopharyngeal carcinoma, the use of neural network on fine needle aspirates for the diagnosis of breast cancer, image enhancements and intelligent screening for breast and cervical cancers, and the search for novel tumour markers (e.g. insulin-like growth factor-1, transforming growth factor-beta 2, glycoproteins, p53 autoantibodies, etc).[48,49]

PROGNOSTIC AND PREDICTIVE INDICATORS, AND CANCER PROGRESSION

Prognostic and predictive indicators

Studies into prognostic and predictive indicators encompass another large group of projects with high potential for direct clinical usage, particularly in the planning of cancer therapy. This is exemplified by intensive research on breast cancer in the 7th Malaysia Plan. Early validation studies led to replacement of solid phase enzyme immunoassay (on fresh cytosols) by immunohistochemistry (on paraffin-embedded tissue) for the assessment of oestrogen receptor (ER) protein expression.[50] Subsequent demonstration of a good correlation between expressions of ER protein and the trefoil protein pS2 raised the potential utility of pS2 as a co-marker of endocrine responsiveness in invasive breast cancer.[51] The possibility that the c-erbB-2 oncogene may have both prognostic and predictive roles was mooted by findings that c-erbB-2 overexpression correlated with high histological grade and loss of ER protein in invasive breast cancer. This may help identify subsets of patients for more aggressive therapy.[52]

Other equally relevant studies are those looking into inexpensive, safe and rapid procedures for the prognostication of childhood solid tumours, correlations of abnormal expressions of specific genes with aggressive behaviour in tumours, MLL gene abnormalities as markers of prognosis in acute leukaemias, and the interaction of tumour, host and viral factors in the growth and progression of malignant lymphoma. There is continuing intensive current research into molecular markers and genes, and cell-cycle regulators that may relate to cancer aggressiveness.[53-55] These include N-myc gene amplification in neuroblastoma, mutations of the p53 and bcl2 genes in rhabdomyosarcoma, gene profiling in colorectal carcinoma, gene expression profiles in brain cancer cells in response to tamoxifen and like compounds, and the role of Cyclin D1, vascular endothelial growth factor (VEGF) and CD31 expression in colorectal cancer.

Cancer progression

As tumour progression is one of the most important events leading to morbidity and mortality in cancer patients, attention is drawn to research into the mechanisms of neoplastic invasion and metastasis. A study of malignant odontogenic tumours have suggested that modification and remodeling of basement membrane collagen IValpha chains occur during odontogenic neoplasms' progression.[56] Angiogenesis factors and interactions between cancer cells, basement membrane and extracellular matrix proteins appear to play important roles in this process.[57,58] Ongoing research also investigate the angiogenetic role of endothelins in hepatocellular carcinoma, and chemokines and angiogenetic factors in gynaecological cancers. Such studies into cell-cell and cell-matrix signals may reveal pathways amenable to anticancer modulation.

Cancer immortalization

The unique ability of tumour cells to proliferate indefinitely (immortalization) is crucial to neoplastic progression as it allows these cells to express the aggressive properties of cancer without the censure of physiological ageing. This is in contrast to normal somatic cells which are subject to a "mitotic clock," a phenomenon that has been linked to telomeric shortening after each round of cell replication. Studies at the Department of Pathology, University of Malaya have investigated the role of telomerase, an enzyme that synthesizes telomeric material, in immortalization of breast, cervical and colonic cancer cells, using a combined Polymerase Chain Reaction and Enzyme Link Immunosorbent Assay (TRAP-ELISA). Telomerase activity was demonstrated in 20-60% of neoplastic tissue samples whereas non-neoplastic controls showed almost no telomerase activity. That the differential presence of telomerase may provide a potential basis for anti-neoplastic chemotherapy and the feasibility of using telomerase assay as an adjuvant marker of malignancy have been mooted.[59-62]

RESEARCH OUTPUTS

Patents, papers and resource development

While the above accounts of some of the research activities in cancer diagnosis may give an indication of output, it must be noted that most recent research findings under the 8th Malaysia Plan are not yet ready to be reported or published. A summary of output based on 60 recent and current projects is shown in Table 7. It is very likely that this is a gross underestimation of the number of papers and publications that have resulted from research in the 7th and 8th Malaysia Plans. However, it is noteworthy that a lot of research findings presented at scientific meetings have not yet found their way to publication, suggesting work overload in mature researchers and lack of writing experience in young researchers. Nevertheless, based on the output

revealed in Table 7, we expect a fruitful outcome from 8th Malaysia Plan projects, especially from University researchers.

The gross shortage of patents and commercialization of research findings (such as creation of test kits) appears rather glaring. More information needs to be gathered to understand the problems faced by researchers in this area.

Experience gained with the new technologies utilized in cancer diagnosis research have increased the technical expertise of Malaysian cancer researchers and allowed adaptation of new technologies into the local setting. Examples are successes scored in the application of in-situ hybridization, flow cytometry and other molecular techniques on paraffin-embedded tumour material, allowing analysis to now be carried out on archival tissues.[63-70] The

Table 7: Summary of Output from Recent and Current Cancer Diagnosis Research Projects

Patents	1
Papers • Publications • Presentations	 94 209
Human resource development • MSc • PhD	 51 21
International linkages	• University of Oxford, UK • University of London, UK • University of Bristol, UK • University of Birmingham, UK • University of Liverpool, UK • Guy's, King's & St Thomas's, London, UK • University of Groningen • Karolinska Institute, Sweden • Huntington Medical Research Institutes, Pasedena, USA • University of South California, USA • Queensland Institute for Medical Research, Australia • Murdock Children's Research Institute, Melbourne, Australia • Kaohsiung Med College, Taiwan • University of Indonesia • University of Trisakthi • University of Hong Kong • Manipal Academy of Higher Education, India • Kandang Kerbau Woman and Children's Hospital, Singapore • National University of Singapore

application of computerized analyses of cancer images is another example.[71]

The number of young scientists (MSc and PhD) being currently trained through cancer diagnosis research projects are encouraging (Table 7). Furthermore, the training of these young scientists in research ethos is an important investment towards the creation of a good research culture. This cannot be easily quantified but is, nonetheless, extremely important for the future of cancer research in this country. However, it has not been ascertained how many of our research assistants go on to pursue a career in research within this country. A survey into this aspect may reveal objective information on which future strategies can be based.

National guidelines and consensus development

Because diagnosis is very much a part of clinical practice, many researchers have indicated satisfaction and confidence that their work will be translated into practice and will significantly improve the diagnostic services in Malaysia. It is noteworthy that National guidelines and consensus development on at least three malignancies i.e. breast cancer, oral cancer and lymphoma, have substantial basis in local research and development work.[72-74]

International linkages

Collaboration between local researchers and International centres are very much based on personal contact and mutual interest of researchers. In view of our strong traditional links with the United Kingdom, it is not surprising that most existing collaborations are with British Universities (Table 7). This has helped local researchers to "catch up" with new technology through technology transfer and building of confidence in research capability. International comparison studies can also help to highlight Asian and Malaysian findings as well as contributed to global knowledge of cancer.

PROBLEMS ENCOUNTERED

As there was poor response to a survey on problems encountered in research, there is no quantifiable objective information on problems faced by researchers. Among those identified were:

1. Insufficient funding to realize the research objectives
2. Lack of expertise within the country (most research assistants are inexperienced BSc graduates with no or minimal research experience. Very few research assistants are at PhD level)
3. Inadequate technical support from vendors during equipment failure.
4. Inexperienced Institutional business development units to assist in product development
5. Lack of venture capital for commercialization of findings
6. Inadequate incentives to undertake research

CHALLENGES AND PLAN TO PROMOTE RESEARCH

1. The need for Cancer Tissue Banks

Many researchers have pointed out the need for cancer tissue banks to fast-track and co-ordinate cancer research. An IRPA-funded project, led by the University of Malaya, will be initiating a database and tissue resource bank for oral cancer and precancer research. USM has established, in collaboration with MINT, a National Tissue Bank with repositories of bone, amnion and skin. However, a National or Regional Cancer Tissue Bank has yet to be realized.

2. A National Cancer Research Institute

The establishment of a National Cancer Research Institute as a Centre of Excellence may serve to provide the impetus for a concerted effort against cancer, in a spirit of competition and collaboration. We envisage an Institute where research drives all aspects of cancer management, whether it be in the areas of prevention, diagnosis, cancer biology, anticancer therapy, clinical trials, etc.

3. A Dedicated Cancer Research Fund

A dedicated cancer research fund can be justified due to the National importance of cancer. This should be separate from IRPA funding because the outcome objectives are different, being measured more in terms of benefits to patients and healthcare rather than commercialization of products. However, like IRPA, we envisage that this fund should be awarded through an appropriate Government body (such as Ministry of Health, MOSTI or the Prime Minister's Department). It should be open to all cancer researchers in Malaysia. The management body should have fair representation from all bodies with an interest in cancer, such as the Ministry

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of Health, Universities and Non-Governmental Organisations. Members of the technical evaluation panels should have research expertise and be knowledgeable in cancer biology.

4. Registry of cancer researchers

The establishment and maintenance of a registry of cancer researchers and projects will improve networking among researchers. In the presence of limited resources, redundant and repetitive research on the same subject matter by different research groups may not be justified. The registry should capture all present and past cancer research projects carried out in Malaysia, including contact details of researchers, research objectives and details of outcome. Information should be available online.

5. Research coordination

It is recognized that the keen sense of competition among researchers have a dark side resulting in territorial behaviour, distrust and poor etiquette amongst them. There is also a notable gap between medical and non-medical researchers and between patient-orientated and laboratory-oriented researchers, in terms of lack of cooperation and appreciation of each other's roles. The National Cancer Research Coordination Committee may serve to promote a culture of openness, ethical research and effective collaboration through a network of research coordinators. Each coordinator should coordinate research into a particular targeted cancer, with the aim of encouraging different groups to work on different aspects of the targeted cancer, to avoiding duplication of research and wastage of resources. To be able to play such a role effectively, he should preferably be a respected senior researcher with good diplomatic skills, identified by the researchers themselves, and backed by secretariat resources. It is important that the research coordinator is not perceived as someone who holds the largest research grant or controls the approval of research funds, as this may lead to suspicions of nepotism and cronyism.

6. Improve coverage of National Cancer Registry

While the newly created National Cancer Registry is an encouraging and much welcome development for cancer researchers, it is recognized that the data captured needs to be broader.

7. International collaboration

More active collaboration with experienced researchers in technological advanced countries, particularly in the United States, may further enhance technology transfer and development of technological expertise. There should be more institutional support for sending young researchers to undertake the whole or part of their MSc or PhD training in overseas centres

8. Development of a better career structure for researchers

This may be crucial if the country is to retain its young scientists within the active research workforce. It is perceived that many research assistants leave the country for greener pastures after obtaining their PhD from Malaysia. Currently there are limited research officers positions within designated Research Institutions. The creation of such posts within the Universities and even hospitals should be seriously considered in the fight against the "drain" of young researchers as well as to boost research commitment.

9. Institutional support for product realization

The development of more effective business units within research institutions and the Universities is imperative for realization of the commercial potential of research findings. The protection of the intellectual property rights of researchers, and financial benefits are vital incentives.

10. Recognition for cancer researchers

A number of cancer research findings have received prizes and medals at various national and international arenas. Within the ranks of Malaysian cancer researchers are a National Science Laureate, an Asean Outstanding Scientist, Fellows of the Academy of Sciences Malaysia, National young scientists, Tun Abdul Razak Research Awardees and Toray Foundation Research Grantees. However, these represent recognition within the scientific community. Public recognition of medical research excellence remains discouraging.

CONCLUDING REMARKS

As Malaysia progresses towards the status of a developed, technologically-advanced country, so too should its medical research environment and culture. In addressing the challenges posed

in the field of cancer research, it would be necessary to draw on the will, not only of researchers, but also of Research Institutions, Universities, Governmental Ministries, Professional bodies and the Public. We believe that as research capability matures, there will be an increasing funding contribution from the private sector, including the pharmaceutical industry. Actual research in the private sector is also envisaged to increase substantially. The development of public-private partnerships in research efforts may eventually be linked to the survival and future of both research sectors.

Professional bodies, such as the Academy of Medicine Malaysia, can play a pivotal role in promoting interdisciplinary medical research. In this regard, the Academy of Sciences Malaysia may also play a significant role in linking the medical and non-medical sciences in joint research effort against cancer.

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