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EVALUATION OF OTX1 AS A POTENTIAL BIOMARKER OF BLADDER CANCER

AMINUDDIN BAHARUDIN

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EVALUATION OF *OTX1* AS A POTENTIAL BIOMARKER OF BLADDER CANCER

By

AMINUDDIN BAHARUDIN

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EVALUATION OF *OTX1* AS A POTENTIAL BIOMARKER OF BLADDER CANCER

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AMINUDDIN BAHARUDIN

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Chair: **Abhimanyu Veerakumarasivam, PhD**
Faculty: **Medicine and Health Sciences**

Bladder cancer ranks as the ninth most frequently-diagnosed cancer worldwide. With no suitable and validated biomarkers of diagnosis and prognosis, patients are plagued with a high risk of recurrence and progression resulting in significantly increased rate of morbidity and mortality. *OTX1* has been implicated as a potential oncogene in several cancers but how *OTX1* actually contributes to bladder cancer formation is still poorly understood. Hence, I aimed to evaluate *OTX1* as a potential biomarker for bladder cancer in this study. To achieve that, I studied the mRNA expression of *OTX1* across a series of bladder cancer cell lines via RT-qPCR and conducted *OTX1* siRNA knockdown to reduce the expression of *OTX1 in vitro*. To observe the effects of knockdown on the migratory rate of cells, migration assay was conducted. The mRNA expression in cancer stem cells *in vitro* and protein expression of OTX1 in bladder cancer tissues was also investigated via RT-qPCR and IHC respectively. In addition, I attempted to discover the potential of *OTX1* as a biomarker of response to predict Newcastle Disease Virus-mediated oncolysis by correlating the expression of *OTX1* with IC_{50} values of cell lines infected with NDV. I found that *OTX1* was expressed in most bladder cancer cell lines. No significant difference in migratory rate was seen when *OTX1* was knockdown in HTB-4. Intriguingly, *OTX1* was significantly overexpressed in spheroid cultures compared to monolayer cultures. Using Spearman correlation, I found significant correlation between the protein expression of OTX1 with grade 2 and 3 bladder tumours and using Pearson correlation, weak correlation was found between the fold changes of *OTX1* with the IC_{50} values across similar bladder cancer cell lines. Continuing to expand the findings from this study may lead to a deeper and clearer understanding of the potential role of *OTX1* as a biomarker for bladder cancer management.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia
sebagai memenuhi keperluan untuk ijazah Master Sains

PENILAIAN *OTX1* SEBAGAI PENANDA BIOLOGI BERPOTENSI UNTUK KANSER PUNDI KENCING

Oleh

AMINUDDIN BAHARUDIN

Oktober 2018

Pengerusi: **Abhimanyu Veerakumarasivam, PhD**
Fakulti: **Perubatan dan Sains Kesihatan**

Kanser pundi kencing merupakan kanser kesembilan yang paling kerap didiagnosis di seluruh dunia. Dengan ketiadaan penanda biologi yang sesuai dan sah untuk kegunaan diagnosis dan prognosis, pesakit dibelenggu dengan risiko tinggi untuk kanser muncul semula dan maju ke tahap lanjut yang seterusnya meningkatkan kadar morbiditi dan mortaliti. *OTX1* berpotensi sebagai onkogen dalam beberapa kanser namun bagaimana *OTX1* sebenarnya menyumbang pada pembentukan kanser pundi kencing masih belum difahami sepenuhnya. Oleh demikian, saya ingin menilai potensi *OTX1* sebagai penanda biologi untuk kanser pundi kencing dalam kajian ini. Untuk mencapai matlamat tersebut, saya mengkaji ekspresi mRNA *OTX1* dalam beberapa siri sel selayar kanser pundi kencing menggunakan RT-qPCR dan melakukan *OTX1* siRNA *knockdown* untuk mengurangkan ekspresi *OTX1 in vitro*. Untuk mengkaji kesan *knockdown* ke atas kadar migrasi sel, saya melakukan asai migrasi. Ekspresi mRNA dalam sel stem kanser *in vitro* dan ekspresi protein OTX1 dalam tisu kanser pundi kencing telah dikaji menggunakan RT-qPCR dan IHC. Selain itu, saya hendak mengenal pasti jika terdapat potensi untuk *OTX1* menjadi penanda biologi tindak balas untuk menjangka onkolisis dengan Newcastle Disease Virus sebagai pengantaranya dengan mengenalpasti korelasi antara ekspresi *OTX1* dengan nilai IC_{50} siri sel selayar yang dijangkiti NDV. Saya mendapati *OTX1* diekspresi dalam kebanyakan sel selayar kanser pundi. Tiada perbezaan yang ketara dalam kadar migrasi setelah melakukan *OTX1 knockdown* ke atas HTB-4. Menariknya, *OTX1* diekspresi sangat tinggi dalam kultur sferoids berbanding dengan kultur selayar. Dengan menggunakan korelasi Spearman, saya menemui korelasi antara ekspresi protein OTX1 dengan tumor pundi kencing gred 3 dan gred 2. Menggunakan korelasi Pearson pula, hampir tiada korelasi antara ekspresi *OTX1* dengan nilai IC_{50} dalam semua sel selayar kanser pundi kencing. Usaha yang berterusan dalam mengembangkan penemuan kajian ini mampu membawa kepada pemahaman yang lebih jelas dan mendalam akan potensi *OTX1* sebagai penanda biologi untuk kanser pundi kencing.

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The thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

Abhimanyu Veerakumarasivam, PhD
Senior Lecturer
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Datin Paduka Khatijah Yusoff, PhD
Professor
Faculty of Biotechnology
Universiti Putra Malaysia
(Member)

Chan Soon Choy, PhD
Associate Professor and Dean
School of Foundation Studies
Perdana University
(Member)

_____
ROBIAH BINTI YUNUS, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

Date:

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Signature:_____
Name of Chairman of
Supervisory Committee: Abhimanyu Veerakumarasivam,

Signature:_____
Name of Member of
Supervisory Committee: Datin Paduka Khatijah Yusoff

Signature:_____
Name of Member of
Supervisory Committee: Chan Soon Choy

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LIST OF ABBREVIATIONS

±	Plus minus
°C	Celcius
µL	Microliter
µm	Micrometer
3-D	3 dimensional
ACC	Adenoid cystic carcinoma
AJCC	American Joint Committee on Cancer
ATV	Autologous tumour cell vaccine
b-FGF	Basic fibroblast growth factor
BCG	Bacillus Calmette-Gu´erin
BR	Biological replicate
cDNA	Complementary deoxyribonucleic acid
CI	Contact inhibition
CGI	CpG island
CO_2	Carbon dioxide
CSC	Cancer stem cell
Ct	Cycle threshold
DDR	Durable disease response
DNA	Deoxyrobonucleic acid
EDTA	Ethylene-diamine-tetra-acetic acid
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EMX	Empty spiracles homeobox
EMT	Epithelial-mesenchymal transition
FBS	Fetal bovine serum
FFPE	Formalin-fixed paraffin embedded
FGFR	Fibroblast growth factor receptor
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
GF	Growth factor
HOX	Homeobox
HRAS	HRas proto-oncogene GTPase
HCC	Hepatocellular carcinoma
IC	Inhibitory concentration
IFN	Interferon
IHC	Immunohistochemistry
IRS	Immunoreactive score
ISUP	International Society of Urological Pathology
Kb	Kilobase
MAPK	Mitogen-activated protein kinases
MIBC	Muscle-invasive bladder cancer
miRNA	Micro RNA
mL	Milliliter
mRNA	Messenger RNA
ng	Nanogram
nm	Nanometer
NMIBC	Non-muscle invasive bladder cancer
NDV	Newcastle disease virus
OTX1	*Orthodenticle homeobox* 1

OV	Oncolytic virus
p53	Tumour protein 53
PAX	Paired box
PBS	Phosphate buffered saline
PCG	Polycomb group
PCR	Polymerase chain reaction
PIK3CA	Phosphoinositide-3-kinase, catalytic, alpha polypeptide
PTEN	Phosphatase and tensin homolog
Rb	Retinoblastoma
RCF	Relative centrifugal force
RNA	Ribonucleic acid
ROM	Rate of migration
RT-qPCR	Real-time quantitative PCR
SC	Stem cells
SD	Standard deviation
SDHA	*Succinate Dehydrogenase Complex Flavoprotein Subunit A*
siRNA	Small interfering RNA
SMT	Somatic mutation theory
T-Vec	Talimogene laherparepvec
TBE	Tris/Borat/EDTA
TBP	*TATA-binding protein*
TBS	Tris-buffer saline
TCC	Transitional cell carcinoma
TNM	Tumour-node-metastasis
TOFT	Tissue organization field theory
TRAIL	TNF-related apoptosis-inducing ligand
UV	Ultra-violet
VEGFR	Vascular endothelial growth factor receptor
WB	Western blot
WHO	World Health Organisation

CHAPTER 1

INTRODUCTION

1.1 Background

Cancer is not a recently discovered disease. Cancer dates back to 1600 B.C. in Egypt where descriptions were transcribed on papyrus. Breast tumours were treated by cauterization while stomach cancer with boiled barley mixed with dates (Akulapalli, 2009). However, the understanding of cancer has never been as paramount as it is now owing to the increase in global population aged 60 or above (United Nation, 2017) which in turn contributed to cancer being the number one cause of death worldwide. Despite rapid improvements in cancer research the past several decades, it is estimated that approximately 15 million new cancer cases will be diagnosed by 2020 and from that number, only 3 million will survive (Bray and Moller, 2006). 90% of cancers are either solely due to environmental factors, or a result of the interaction between genetic and environmental factors while only 5–10% of cancers are attributed to genetics. The most common genetic lesions are related to oncogenes and tumour-suppressor proteins such as p53 and retinoblastoma (Rb) protein, but no two cancer profiles are the same. Type of cancers include breast cancer, lung cancer, liver cancer, and bladder cancer.

Worldwide, bladder cancer ranks as the ninth most frequently diagnosed cancer with a higher incidence rates observed in men compared to women. It is also the thirteenth cancer with highest rate of mortality (Antoni *et al.*, 2017). There are two forms of bladder cancer, non-muscle invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) (Cancer Research UK, 2015). The high mortality and low survivability rate of MIBC calls for constant monitoring on NMIBC to prevent possible recurrence and progression to MIBC (van Rhijn *et al*., 2009). Non-invasive tumours are found to contain defects in the HRas proto-oncogene GTPase (HRAS) and fibroblast growth factor receptor 3 (FGFR3) while its invasive counterpart is due to mutations in the p53 and pRb pathways (Wu, 2005). There are several types of bladder cancer and the most common is transitional cell carcinoma (TCC), accounting for 90% of bladder cancer. Normally, patients with TCC are treated through transurethral resection and adjuvant intravesical chemotherapy or immunotherapy, however, the rate of cancer recurrence within 1 to 2 years is high (Babjuk *et al.*, 2013). This does not mean that the remaining 10% of bladder cancer types are insignificant, as most of them can be more aggressive and present higher mortality rates (Rogers *et al*., 2006; Wasco *et al*., 2007). Other bladder cancer types include squamous cell carcinoma, urachal carcinoma, small cell carcinoma, micropapillary bladder carcinoma, and several others.

The most common symptom of bladder cancer is hematuria. An estimated 20% of patients experiencing macroscopic haematuria will be diagnosed with bladder cancer (Bruyninckx, 2003). Other symptoms include dysuria, flank pain, and urinating small volumes frequently. A number of risk factors may contribute to someone being afflicted with bladder cancer. As with other cancers, age is a risk factor, occurring more commonly in the elderly than in young people. The highest risk factor however is

cigarette smoking with a population attributable risk of 46% (American Cancer Society, 2009). Occupational exposure to aromatic amines and other carcinogens also poses significant risk factors, such as in the painting and leather industries, rubber manufacturers, and factory workers (Vineis and Piratsu, 1997; Delclos and Lerner, 2008). Urinary tract infection by *Schistosoma haematobium* and a non-functioning bladder are associated with an increased risk of squamous cell carcinoma (Mostafa *et al*., 1999; Kantor *et al*., 1984). Increasing fluid intake may lower the risk of bladder cancer by increasing urine output and decreasing exposure of the bladder to carcinogens. Increasing fluid intake also dilutes the concentration of carcinogen in the bladder (Michaud *et al*., 1999; Leppert *et al*., 2006).

The major hurdle with bladder cancer is its high risk for recurrence and progression to muscle-invasive disease and subsequent metastasis resulting in poor clinical outcome (van Rhijn *et al*., 2009). Although 75% of newly diagnosed cases are NMIBC, despite medical intervention, up to 50% will recur and 25% will progress to MIBC (Kamat *et al*., 2017). As mentioned before, patients with MIBC have low survivability rate. This is due to the tumour being resistant to both chemotherapy and radiotherapy, posing a significantly higher risk of metastasis (Drayton and Catto, 2012). Moreover, lifetime surveillance and treatment for recurrent tumours are only two of many reasons why bladder cancer has the highest cost of treatment of any malignancy per patient itself (Darwiche, 2015). Thus, early and accurate detection is vital to secure an improved quality of life to these patients.

One of the methods to detect bladder cancer is cystoscopy which is invasive and expensive (Lotan and Roehrborn, 2002). An alternative, non-invasive and inexpensive method is detection through voided urine (Nielson *et al*., 2006) but one of its biggest disadvantage is poor sensitivity for low-grade bladder cancer (Lokeshwar *et al*., 2005). As more markers for bladder tumour are tested and validated, the efficacy of urine cytology will certainly increase as seen in recent studies such as done by Beukers *et al*., (2017), presenting patients with a non-invasive, inexpensive, and highly sensitive method for bladder cancer detection and diagnosis.

Expression of a specific cancer or tumour releasing products are some characteristics of an ideal biomarker. One gene that exhibits these characteristics is *orthodenticle homeobox* 1 (*OTX1)*, a member of the homeobox gene family and is a transcription factor. *OTX1* gene is a vertebrate orthologue to the *Drosophila* and expressed during the development of *Drosophila* head. *OTX1* has a number of orthologues, but the defining function they have in common is its expression during early embryonic brain development (Li *et al*., 1994; Kablar *et al*., 1996: Acampora and Simeone, 1999). Defects in the gene lead to multiple complications of the brain such as reduced cortical thickness and hypogonadism (Acampora *et al.*, 1996: Zhang *et al.*, 2015). *OTX1* is found on chromosome 2, mapped at 2p13 (Kastury *et al.*, 1994). Based on several studies, there are high expressions of *OTX1* in several cancers such as colorectal cancer (Yu *et al.*, 2014), breast cancer especially invasive breast cancer (Pagani *et al.*, 2010) and hepatocellular carcinoma (HCC) (Li *et al*., 2016). Recently, an accurate prediction model for bladder cancer was developed by coupling *OTX1* with several other genes and running methylation analysis, providing a sensitivity of 97% and a specificity of 82%

(van Kessel *et al*., 2016). All these findings point to *OTX1* being a potentially important biomarker for bladder cancer, both diagnostic and therapeutic.

Another agent that plays an important role in treating bladder cancer is Newcastle Disease Virus (NDV), a paramyxovirus that causes Newcastle disease in a wide variety of avian species but is harmless to human. Many studies proposed NDV as a potential anticancer agent due to its ability to target and kill cancer cells. The first report of positive results using NDV was to treat a patient with acute leukemia and was published in 1964 by Wheelock and Dingle. The fact that both lytic and non-lytic (Matveeva *et al*., 2015) strains of NDV can replicate better in human cancer cells than in most normal human cells by exploiting the defects in the intracellular antiviral defences of some cancer cells has garnered much interest on it being a potential anticancer agent. Mechanisms of NDV oncolytic activity include direct killing by syncytium formation and an indirect mechanism via antitumoral immune response activation (Anderson *et al*., 2004; Zamarin and Palese, 2012).

As with different types of cancer needing different kinds of treatments, the same applies with NDV. The heterogenous nature of cancer means that one successful outcome using NDV may have no effect on another patient as no two cancers are alike. Rather than depending on trial and error, this can be overcome with biomarkers. Certain biomarkers may indicate how well a tumour will respond to a treatment.

In this study, I am going to study the differential expression of *OTX1* in bladder cancer and find out if it is a potential biomarker not solely for bladder cancer, but also as a biomarker that can predict the response of bladder cancer towards Newcastle Disease Virus-mediated oncolysis.

1.2 Problem Statement

There is a high risk of bladder cancer recurrence and invasion but no suitable biomarkers have been found to predict recurrence, invasion or treatment efficacy of bladder cancer. Although *OTX1* has been identified as a potential biomarker for the detection of bladder cancer, how the gene contributes to bladder cancer formation is yet to be discovered. There are also no studies on the effect of modulating the expression of *OTX1* in bladder cancer cells *in vitro*. Furthermore, here are no known biomarkers to predict bladder cancer response to NDV-mediated oncolysis,

1.3 Hypothesis

In this study, it is hypothesised that *OTX1* is differentially expressed in different bladder cancer cell lines and in spheroids. Furthermore, a higher percentage of high grade and late stage tumours express OTX1 as compared to low grade and early stage tumours is hypothesised. It is also hypothesised that there is a correlation between the expression values of *OTX1* and sensitivity towards NDV-mediated oncolysis, and that the

knockdown of *OTX1* gene will reduce the expression of *OTX1* and affect bladder cancer migration *in vitro.*

1.4 Objectives

1.4.1 General Objective

The main objective of this study is to evaluate *OTX1* as a potential biomarker in bladder cancer.

1.4.2 Specific Objectives

The specific objectives of this study are:

I. To determine the expression of *OTX1* in bladder cancer cells *in vitro.*
II. To compare the expression of *OTX1* in spheroids and in monolayer cells *in vitro*.
III. To downregulate the expression of *OTX1* in highly-expressing bladder cancer cells *in vitro.*
IV. To determine the effect of modulating *OTX1* expression *in vitro* on the migratory potential of bladder cancer.
V. To identify the protein expression of OTX1 in bladder cancer tissues and correlate it with bladder tumour stages and grades.
VI. To evaluate the correlation between the expression of *OTX1* and cellular sensitivity towards NDV-mediated oncolysis.

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BIODATA OF STUDENT

Aminuddin Baharudin was born on January 10th 1992 in Pahang, Malaysia but was brought up in Terengganu, Malaysia. After completing Sijil Pelajaran Malaysia in Sekolah Menengah Kebangsaan Sultan Ismail II, he pursued Foundation in Science at Universiti Teknologi MARA, Puncak Alam, Malaysia. After a year of foundation studies, he then conducted his Bachelor of Degree (Honors) at Universiti Putra Malaysia (UPM) on September 2011, majoring in Biology. Haven't yet discovered his interest, he took different elective subjects and found what he was looking for in genetics.

With this in mind, he wanted to continue his Masters' Degree in genetics but decided to work for a year as a research assistant for a Down syndrome project under Dr. Michael Ling King Hwa of at Faculty of Medicine and Health Science, UPM. He took this time to research on what aspects of genetic studies truly resonates with him and stumbled upon cancer research.

Having always wanted to have a career that gives back to the people, he felt a strong connection to cancer genetics. With the right foot forward, he pursued his Masters' Degree on September 2016 under the supervision of Prof. Dr. Abhimanyu Veerakumarasivam of Faculty of Medicine and Health Science, UPM. Throughout his masters' studies, not a single moment passed by that took his spark and drive away from his research. He aspires to obtain a professorship and use his knowledge to pump out meaningful and significant research to aid the field of cancer genetics.

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