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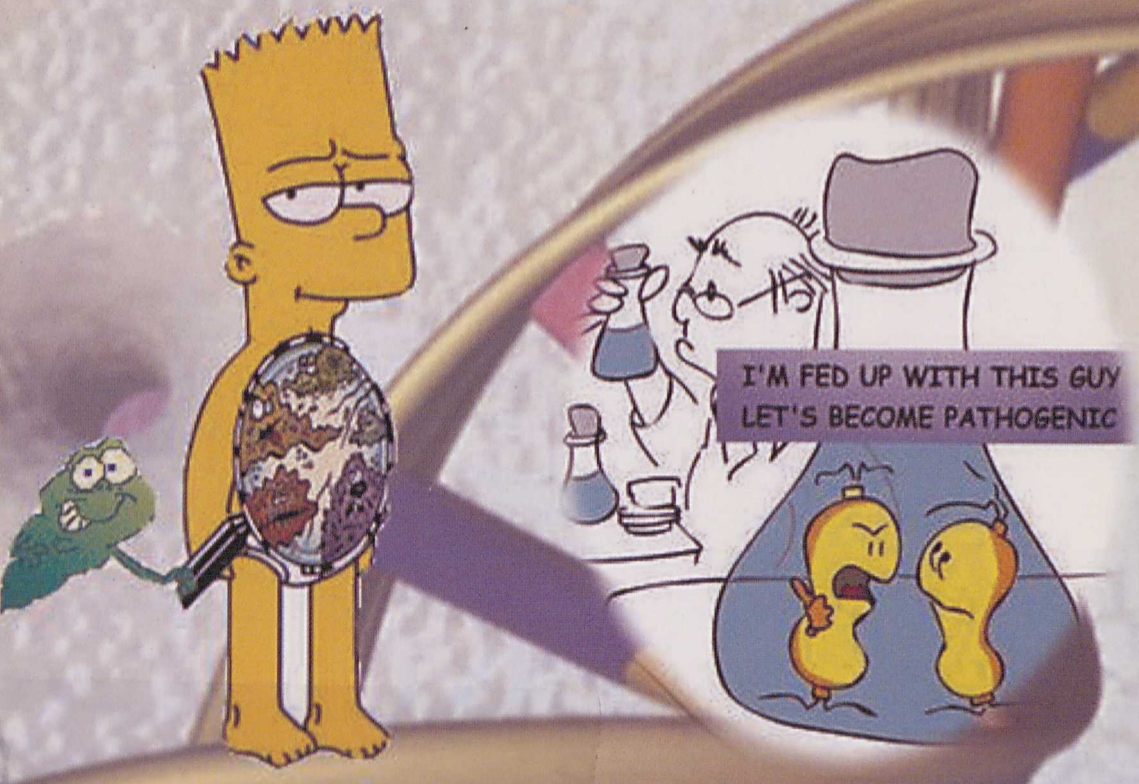
INAUGURAL LECTURE

THE ENEMY WITHIN: MICROBES AND GENES



10 December 2009

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16th December 2009

By:

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Syarahan Perdana ini diadakan sebagai pengiktirafan jawatan profesor di Universiti Malaya

Professor Dr. Jamuna Vadivelu

Professor Dr Jamuna Vadivelu was born in Petaling Jaya and completed her schooling at the Assunta Secondary School, Petaling Jaya. She went to the UK to undertake her A-level programme and obtained the Bachelor of Science Degree in Microbiology with Honours from the University of Surrey, Guildford UK in 1982. She continued on at the University of Surrey, Guildford, UK, to work for a year during which time she obtained a Medical Research Council grant to pursue work on Enterotoxigenic *Escherichia coli* for her PhD at the London School of Hygiene and Tropical Medicine, University of London. She obtained her PhD in 1987 and was a Post-doctoral Fellow at the University of Maryland, USA until she joined as a lecturer at the Department of Medical Microbiology, University of Malaya in 1989. She was promoted to Associate Professor in 1998 and went on to obtain a Master of Science in Computational Genetics and

Bioinformatics from the Imperial College of Medicine, Science and Technology, University of London in 2002. In 2003 she was promoted to Professor.

During her career she has obtained many awards and fellowships. These include:

- Metal Box Award, UK
- Association of Commonwealth Universities, UK Travel Fellowship
- Swedish Institute Guest Fellowship
- Marie Curie Award, European Union Fellowship
- British Chevening Scholarship
- FAIMER Institute Fellowship
- Australia-Malaysia Institute Fellowship

Prime Minister's Award for Research Invention between the Public and Private Sector,
Silver Medal for Melioidosis Diagnostic Kit, International Trade Exhibition (ITEX), Malaysia
Silver Medal for Melioidosis Diagnostic Kit, MOSTI Silver Jubilee Exhibition, Malaysia

Her research interests are wide, varied and include:

- Environmental detection of Enterotoxigenic *Escherichia coli*
- Virulence factors of *Aeromonas hydophila*
- Molecular epidemiology and the role of the environment on the survival and virulence of *Vibrio cholerae*.
- Human melioidosis: diagnostics, pathogenesis and vaccine development.
- Bioinformatics and Functional Genomics -Investigating functional genomics of virulence genes of microbial pathogens.
- Familial Hypercholesterolemia: Development of a microarray base chip for the diagnosis of familial hypercholesterolemia in the Malaysian population.
- Diabetes Mellitus - Development of molecular screening

kit for diagnosis and management of diabetes mellitus (type2) in Malaysian population.

- Immune modulation of cancer - novel endogenous proteins released from cancer cells following HIFU as immunotherapeutics.
- Medical Education- Assessing the integration of basic sciences in clinical teaching.

She has been involved in teaching programmes in the University, supervised postgraduate and post-doctoral students, presented papers in international and local meetings and published in peer-reviewed international journals. She is also a member of professional organizations and has collaboration with other universities locally and internationally that include the University of Standford, USA, the Consortium of Glycomics, USA, Monash University, Australia, and Imperial College, UK.

THE ENEMY WITHIN: MICROBES AND GENES

Synopsis:

Life as we know would not exist without bacteria to decompose waste and dead organisms. These bacteria ensure that the cycle of chemical exchange between organisms and their environment is continuous. The environment plays a critical role as a source for the emergence of pathogens and in the manifestation, course, and prognosis of human and animal diseases. Bacteria survive in a host of environmental niches such as soil, surface waters, plants, and in humans. In each of these niches they have specific roles in order to survive. Amongst environmental factors the physiological characteristics, temperature and humidity are critical. In the host, the pathogen is faced with the same ordeal of having to cope with the host physiological parameters as well as the immune system. In order to initiate pathogenesis a bacterium must enter, attach, colonise, multiply and spread. Once the bacterium enters it attaches to specific receptors on the target cell by means of adhesive factors to establish and colonise, and some may survive intracellularly for long periods of time. Various proteins are then secreted to initiate the process of survival within the host. These proteins have diverse biological functions ranging from host cell toxicity to more subtle alterations of the host cell for the benefit of the invader and are of immense value for diagnostic markers, drug design and vaccine development. Important questions directed throughout the course research include: Is the environment a source for some of the pathogens addressed? What are the factors that favour survival of the pathogen in the environment and in the host and where are the occult foci in the host? What are the bacterial proteins that aid the bacterium to invade and survive?

More recently, with the availability of the human genome, on the horizon is a new era of molecular medicine characterized less by treating symptoms and more by looking to the most fundamental causes of disease. Rapid and more specific diagnostic tests can make possible earlier treatment of countless maladies. In addition it would be possible to devise novel therapeutic regimens based on

new classes of drugs, immunotherapy techniques, and avoidance of environmental conditions that may trigger disease, and possible augmentation or even replacement of defective genes through gene therapy. Questions have been directed to two diseases, familial hypercholesterolemia and diabetes mellitus. What are the gene polymorphisms that have occurred within our diverse population in Malaysia among genes for both these diseases? From this information can we target personalized medicine to individuals?

Introduction

Bacteria are the most numerous organisms and the first evolved species on earth. Part of what makes them so ubiquitous is their ability to inhabit many different types of environments including soil, water, air, plants, animals and human. In fact, some species of bacteria are among the hardiest organisms known to man, and can survive in places where no other organism can. Although they exist as normal flora in these environments, we do not know what environmental factors influence their presence in these niches.

Secondary to this, while most bacteria are harmless to humans, some of these can become extremely pathogenic when they move from one environment to man or animal. Pathogenesis of disease or the mechanism by which disease is caused is to understand the way bacteria interact with the host in the causation of disease. Central to this investigation is an understanding of what gene products are required and expressed during a natural infection and how this expression changes over time (from initial adherence, colonization, invasion, spreading of the pathogen intercellularly and cause damage to the host). There are many factors that assist in the survival of these bacteria. We thus endeavor to understand the pathogenesis of bacterial infection which will enable us to find means and ways to eradicate these pathogens e.g. vaccine development and drug therapy.

- What are the influences of environmental factors on pathogens?
- How do bacteria respond to the host environment during an infection?
- How do the pathogens invade, survive and persist in host?
- How do the host factors contribute in defense mechanism against pathogens?
- How do the pathogens interact with the host?
- Future directions and initiatives

What are the influences of environmental factors on pathogens?

To survive in the environment, bacteria must respond to a variety of physical and chemical variables such as temperature, pH, low or high dissolved oxygen concentration, salt concentration and nutrients. To detect the presence of these disease causing organisms and to differentiate these organisms from non-pathogenic forms it was necessary to develop assays that could only detect pathogenic strains of interest.

- **Development of assays for environmental detection of bacteria**

Detection of pathogenic strains of bacteria in the environment is often difficult because of the large number of different bacterial species that exist in the environment. Initial work was designed to detect toxigenic *Escherichia coli* from environmental samples in and at the same time to enable differentiation from non-toxigenic strains that are ubiquitous in environmental water sources. A membrane filter assay for detection of enterotoxigenic *E coli* (ETEC) was developed to investigate it's applicability in transmission and epidemiology studies (Vadivelu et al. 1988).

Identification of environmental sources of ETEC in a Malaysian village was also carried out using selected ETEC assays (Vadivelu et al. 1989). This study was initiated to investigate the importance of water and food in transmission of ETEC. ETEC was detected in all types of samples on at least one occasion in each household. Methods and assays were also evaluated to identify the suitable methods to be undertaken for investigations of ETEC transmission and environmental risk factors (Vadivelu et al. 1988; Vadivelu et al. 1987; Vadivelu et al. 1986). Apart from this, the influence of sodium chloride concentrations and external pH values on the growth and survival of *Vibrio cholerae* was also investigated under controlled conditions in microcosms. *V cholerae* showed specific preferences for the level of sodium chloride and pH values in maintaining the survival capacity. In addition, both internal and external pH levels have also been discovered to some degree of influence on various regulatory mechanisms (Mitin, 1997).

One way in which pathogens evolve is that environmental organisms acquire genes through horizontal transfer that give them an advantage within their non-pathogenic ecosystem. A classic example is the evolution of pathogenic forms of *V cholerae*, non-pathogenic progenitor strains of which are principally found in aquatic ecosystems. Pathogenic strains originate from non-pathogenic strains through a multistep process that includes the acquisition of the type IV toxin-co-regulated pilus (tcp) (Faruque, 2003). Distribution of tcp, the virulence cassette genes, production of haemolysin and protease were investigated among the clinical and environmental origin to assess the pathogenic potential of these strains. An interesting finding was the presence of tcp gene in all our local isolates investigated confirming the environmental transfer of the tcpA virulence gene through the horizontal phage transfer mechanism (Iyer et al. 2000). Molecular analysis of *V cholerae* strains using PFGE and ribotyping demonstrated that in some outbreaks of cholera was due to strains circulating in Malaysia whereas one outbreak due to O139 strain was actually imported from India through Thailand (Iyer & Vadivelu, 2006; Vadivelu & Puthucheary, 2000).

How do bacteria respond to the host environment during an infection?

Bacterial pathogens must be able to gain access, to persist in, and replicate in normally privileged sites within a host. Moreover, they must produce certain factors that result in a level of host damage that perturbs homeostasis. Thus, pathogens must have specific mechanisms for mediating colonization, avoiding the host's immune system, and acquiring necessary nutrients. They must also produce virulence factors that result (directly or indirectly) in host damage. Because the environment encountered within a living host will be quite different from the external environment, pathogens must be able to regulate the necessary genes in coordination as they move from the environment to the host and from one host niche to another.

- **The ability of adherence and invade to host cells.**

The first stage of microbial infection is colonization; the establishment of the pathogen at the appropriate portal of entry. Pathogens usually colonize host tissues that are in contact with the external environment. Sites of entry in human hosts include the urogenital tract, the digestive tract, the respiratory tract and the conjunctiva. Organisms that infect these regions have usually developed tissue adherence mechanisms and some ability to overcome or withstand the constant pressure of the host defenses at the surface. Adherence is mediated by adhesins which are surface proteins found in the cell wall of various bacteria. They bind to specific receptor molecules on the surface of host cells and enable the bacterium to adhere intimately to that cell in order to colonize and resist physical removal. In its simplest form, bacterial adherence or attachment to a eukaryotic cell or tissue surface requires the participation of two factors: a receptor and a ligand.

A study was conducted to evaluate the adherence and invasion capacity of clinically important pneumococcal serotypes at different phases to human epithelial cells. On the whole, this study imparts and provides insight into the prospective diversity among different pneumococcal serotypes and their survivability during

exposure to the host cells (Desa et al. 2008a). A specific adhesin, *pspC* in *Streptococcus pneumoniae*, specific for the adhesion to lung epithelial cells was identified using real-time Polymerase Chain Reaction (PCR)-based gene expression analysis (Desa et al. 2008b).

Our group is also working on *Burkholderia pseudomallei* adhesins. One of the possible routes of infection of *Burkholderia* is through inhalation. Therefore, investigating the effect of environmental conditions that are encountered in airway surface liquid (ASL) might provide some clues in understanding of *B pseudomallei* pathogenesis in this chronic condition. The effect of environmental conditions on *B pseudomallei* adherence and ability to invade A549 lung epithelial cells was investigated. Among the conditions of different pH, the presence of glucose, NaCl, KCl, and $CaCl_2$, only glucose and ASL pH showed increased adherence and invasion. This explains the possible mechanism for the risk factor of melioidosis associated with diabetes (unpublished data). Our research team has also found three unique genes BPSL1661, BPSS0663 and BPSS2053 in *B pseudomallei*. These genes were confirmed in the clinical isolates and the sequences have been deposited at the Genbank database repository. Expression analysis of glucose treated *B pseudomallei,* demonstrated the upregulation of BPSL1661 gene. Therefore, it may be postulated that this gene may be associated with recrudescence of melioidosis in diabetic patients (unpublished data).

One of the features of *B pseudomallei* is the ability to recrudesce and cause recurrent infections. In order to investigate if this phenomenon was due to the ability of the bacterium to persist intracellulary, the constancy of strain genotypes of multiple isolates of *B pseudomallei* from patients with melioidosis was examined by *Bam*HI ribotyping and pulse-field gel electrophoresis (PFGE) of *Xba*I digested DNA. Variation was observed in PFGE pattern of primary and relapse isolates of another patient but this was insufficient to define genetically distinct strains. We concluded that most patients with single and multiple episodes of melioidosis retained a single strain (Vadivelu et al. 1998). This finding has now enabled us to investigate further both in animal

and tissue culture models as to the occult foci of persistence and survival of these bacteria. Recently, our group has demonstrated that *B pseudomallei* have the ability to translocate into the nucleus of the host (manuscript in press).

- **Enzymes and other secreted products**

Bacteria secrete extracellular proteins into the external environment for survival and adaptation. In vitro cultivation of bacteria results in the accumulation of a complex set of proteins collectively termed as the culture filtrate or secretory proteins in the extracellular milieu. Many, but not all culture filtrate proteins are key virulence factors required for pathogenesis of infection.

Early studies were designed to investigate the possible virulence factors involved in bacteraemia caused by *Aeromonas hydrophila* (Vadivelu et al. 1991; Vadivelu et al. 1995). Cytotoxin and haemolysin were found to be produced in combination in the majority of clinical isolates suggesting that this might be an inherent property of *A hydrophila*. However, enterotoxin production was not detected in all the bacteraemic strains. These suggest that although the gene that encodes for enterotoxin production has been shown to be chromosomal but the gene may be cryptic, absent or present on transposon(s) with reverse integration and expression of this property may not be necessary in the pathogenesis of *A hydrophila* bacteraemia. We also demonstrated that the agar plate method is an easier and more suitable alternative method to rabbit erythrocyte assay for detection of hemolysins of *Aeromonas spp.* (Vadivelu et al. 1992). A study was also performed to investigate the distribution of thermostable direct hemolysin (TDH) and TDH-related haemolysin (TRH) using various assays and to determine whether the tdh/trh genes were situated within the chromosomal or plasmid DNA. The findings of this study indicate that in Malaysia, *V parahaemolyticus* should be considered as one of the important etiological agents of diarrheal disease (Vadivelu et al. 1996).

Comparative analysis of extracellular enzymes and virulence exhibited by *B pseudomallei* from different sources was also

investigated (Vellasamy et al. 2009). Enzymes, such as phospholipase C, catalase, phosphatase, protease, superoxide dismutase and peroxidase in the culture filtrate of *B pseudomallei* isolates from different sources were profiled at different time points of growth. Over time, activity of each enzyme at each time point varied and the profile of secretion were similar among all isolates used irrespective of source (clinical or environmental). Infection studies in ICR mice demonstrated varying degree of virulence induced by the isolates. The catalase, phosphatase and phospholipase C were found to be increased in 60–100% of the isolates post-passage in mice suggesting that they may play an important role in the virulence of *B pseudomallei*.

Bacterial secretory proteins are known to induce immune responses and to possess enzymatic activities associated with pathogenicity. These proteins are known to mediate important host-pathogen interactions and consequently are favored candidates for vaccine development. Proteomics and immunoproteomics have been used to profile and identify the proteins in the secretome of *Burkholderia cepacia* and *B pseudomallei*. The identified immunogenic proteins may be used to cover immunisation for both *B cepacia* and *B pseudomallei* to cross-protect and may help in development of vaccines for melioidosis. These immunogenic proteins were found to be mainly involved in metabolism, information storage and processing and cellular processes (manuscript in press).

How do the pathogens survive and persist in host?

Global approaches have led to the identification of novel genes involved in the host pathogen interactions, and in the post genomic era the challenge faced by biologists is to characterize the genes and their functions. The host-pathogen interactions are dynamic, since each modifies the activities and functions of the other. The

outcome of such a relationship depends on the virulence of the pathogen and the relative degree of resistance or susceptibility of the host, due mainly to the effectiveness of the host defense mechanisms. Infectious disease is a result of an intimate relationship between the pathogen and host. Understanding this complex cross-talk between the host and pathogen is essential to improve our understanding of infectious disease.

Electron microscopic demonstration of the extracellular structure of *B pseudomallei* was also investigated where the preliminary findings of the presence of glycocalyx was observed. The enigma of latency and chronicity of melioidosis is probably due to one or both of the following: (1) polysaccharide layer aids or helps the organism to form microcolonies and (2) the variant lacking in the extacellular polysaccharide layer is probably phagocytosed but escapes killing by the oxidative burst (Puthucheary et al. 1996).

Biofilms consists of layers of bacterial populations adhering to host cells and embedded in a common capsular mass. These biofilms are important in bacterial pathogenesis as they play a central role in helping microbes survive or spread within the host because the biofilm matrix acts as shield (Mohammed and Huenf, 2007; Dunne, 2002) and protecting bacteria from host defenses and antibiotics. Bacteria in biofilms are often able to communicate with one another by a process called quorum sensing and are able to interact with and adapt to their environment as a population of bacteria rather than as individual bacteria. Many Gram-negative bacteria regulate gene expression in response to their population size by sensing the level of acyl-homoserine lactone (AHL) signal molecules which they produce and liberate to the environment. AHL results many biological function in Gram-negative bacteria including biofilm development, conjugation, antibiotic synthesis, extracellular enzyme and exopolysaccaride production and expression of extracellular virulence factors (Song et al. 2004).

The ability of *B pseudomallei* to generate biofilms both in vitro and in vivo has been well documented (Boddey et al. 2006; Taweechaisupapong et al. 2005). Currently we are also investigating the role of biofilms and quorum sensing in the

pathogenesis of melioidosis due to large colony variant (LCV) and small colony variant (SCV) of *B pseudomallei* focusing on the environmental factors that enhances biofilm formation, screening and identification of AHL, isolation of quorum quenching bacteria and identification of genes involved in quorum sensing (unpublished data). Initial investigations demonstrated that biofilm formation was optimal at 30°C, pH 7.2 in LB medium which contained 50mM of glucose suggesting that temperature, pH and hyperosmolarity were found to play a role in biofilm formation of *B pseudomallei*.

How do the host factors contribute in defense mechanism against pathogens?

One of the body's innate defense is the ability to physically remove bacteria from the body through such means as the constant shedding of surface epithelial cells from the skin and mucous membranes, the removal of bacteria by such means as coughing, sneezing, vomiting, and diarrhea, and bacterial removal by bodily fluids such as saliva, blood, mucous, and urine.

Human tissues infected by *B pseudomallei* were observed for the type of inflammation invoked, and for histopathological clues of diagnostic value. The lesions which varied from acute to chronic granulomatous inflammation were not identified as tissue-specific (Wong et al. 1995). Since the initial interaction between the host cell and the pathogen is thought to play a key role in determining the outcome of the infections. Initial work was performed to study the host pathogen interactions. Invasion and intracellular survival ability of *B pseudomallei* and *B cepacia* isolates in tissue culture and mice models was investigated. In order to further characterise this cross-talk, the host genes that are differently expressed and regulated in response to *B cepacia* and *B pseudomallei* secretory proteins and live bacteria will be investigated.

- **Detection and Host Monitoring**

B pseudomallei is known to remain dormant and asymptomatic in human for several years and recurrences can occur if conditions are favorable, e.g. in the event of an immune system insult. Effective treatment and eradication of bacterial infections is crucial for patients in order to eliminate chronic diseases. Careful monitoring of infection by way of monitoring antibody response to specific antigens is one way to decide whether to continue or to terminate antibiotic treatment.

Virulence factors such as haemolysins, enterotoxin and antibodies to these factors may be utilized for the diagnosis of pathogens using immunological assays such as ELISA and immunohistochemistry (Tay et al. 2009; Chenthamarakshan et al. 2001; Chenthamarakshan et al. 2000; Cuzzubbo et al. 2000; Wong et al. 1996; Vadivelu et al. 1992., Vadivelu, 1988; Vadivelu et al. 1987, Vadivelu et al. 1986). An IgM-ELISA using heat-killed whole cells of *B pseudomallei* was developed and compared with an indirect haemagglutination technique (IHAT) and an indirect immunofluorescent technique (IFAT) for rapid detection of melioidosis (Vadivelu et al. 1995). The IFAT is currently used for the detection and monitoring of melioidosis at our centre.

The distribution of antibody response to culture filtrate antigens (CFA) of *B pseudomallei* was examined. All immunoglobulin classes except IgE and IgG subclasses were present in the immunoresponse mounted to secretory antigens of *B pseudomallei*. IgG1 and IgG2 were the predominant subclasses against CFA (Chenthamarakshan et al. 2001a). IgM and IgG based ELISA systems were also developed and it was found to be useful in the diagnosis of both septicemic and localised melioidosis (Chenthamarakshan et al. 2001b; Chenthamarakshan et al. 2001c).

In order to assess the usefulness of immunohistochemistry in the diagnosis of melioidosis, we applied immunoperoxidase techniques to a variety of infected tissues including those infected with *B pseudomallei*. The immunohistochemistry using polyclonal antibodies has a useful role in the diagnosis of melioidosis as the

traditional methods for the confirmation of *B pseudomallei* infection by bacterial culture may take several days and require numerous viable organisms (Wong et al. 1996). An immunochromatographic test for the rapid determination of IgM and IgG antibodies to *B pseudomallei* was evaluated by using sera from bacteriologically confirmed melioidosis patients, high risk and clinically suspected patients along with disease control groups. The PanBio melioidosis IgM and IgG rapid test had equal sensitivity to both bacterial culture techniques and reference IFA (Cuzzubbo et al. 2000).

In order to rapidly detect *B pseudomallei* so that appropriate management therapies may be constituted to limit fatality a molecular based assay was developed. Amongst the *Burkholderia* spp., there is a need to differentiate *B pseudomallei* from *B cepacia* as misidentification could lead to false treatment and mismanagement of the patient. PCR assay targeting three genes *groEL* gene, *B pseudomallei* specific *mprA* gene and *B cepacia* specific *zmpA* gene was developed. This assay was able to detect and differentiate the genus and species in a conventional PCR (Patent No: PI 20083144).

Future Directions and Initiatives

- **Detection of Familial Hypercholesteraemia mutations amongst Malaysian population**

The Human Genome Project has made it clear that alternate mRNA splicing plays a more extensive role in generating functional diversity in humans. As high as 15% of genetic disorders are caused by mutations that alters splicing of genes. Familial Hypercholesteraemia is a genetic disease with high prevalence, difficult diagnosis and high risk of cardiovascular disease. Effective treatment is available when early diagnosis is made. Our aim is to build up of FH disease specific genotypic database representing Malaysian population and in-silico validation of molecular markers.

- **Development of molecular screening kit for diagnosis and management of Diabetes mellitus (type II) in Malaysian population**

Diabetes is a chronic and multifactorial syndrome and its true diagnosis is a challenging task for clinicians under traditional medical care setting. Studies are initiated to identify the inheritance mechanism and genetic effect of allelic variants that are responsible for the disease. Development of molecular detection kit will help in detection of asymptomatic population.

- **Cancer**

Dendritic cell (DC)-based cancer immunotherapies are aimed to augment the cellular mediated immunity of cancer patients to recognize and specifically kill the tumour cells. DCs are potent antigen presenting cells which can present processed tumour antigens to T-cells to induce an effective anti-tumour immunity. Tumour cells are unable to do so as they lack the required immunostimulatory signals. In brief, immature DCs are isolated from patients and induced to achieve maturation in vitro before reinjected into patients. To achieve full brown maturation, DCs require stimulus signals, besides of the released tumour antigens. This requires the tumour cells death to be immunogenic. Recently, HIFU has been discovered to have the ability to induce anti-tumour immune response, besides of its primary cell killing effect in treating cancer patients.

HIFU is a high intensity focused ultrasound treatment which is used to treat solid localized tumour. HIFU treatment is based on thermal impulse (Thermal HIFU) or acoustic cavitation (Mechanical HIFU) to cause tumour cell necrosis. Recent studies found out that HIFU-treated tumour cells are immunogenic as the damaged cells release endogenous danger signals besides of tumour antigens. Endogenous danger signals are crucial in activation of DCs maturation.

In our study, we plan to use mechanical HIFU-treated tumour lysates to activate allogeneic DCs. The resulting activated matured DCs will play an important role for subsequent T-cells priming in-

vivo to kill tumour cells. Ultimately, we hope to improve the clinical outcome of DC-based cancer immunotherapies.

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PERSONAL DATA

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ACADEMIC QUALIFICATIONS

1982	B Sc (Hons) in Microbiology (University of Surrey)
1987	Ph D in Microbiology (London Sch Of Hyg & Trop Med, University of London)
2002	M Sc & DIC in Computational Genetics and Bioinformatics (Imperial College of Science, Medicine and Technology, University of London)

AWARDS

1981	Metal Box Award, UK
1992	Association of Commonwealth Universities,UK Travel Fellowship

	(Visited ICDDRB, Bangladesh and University of Varanasi and Centre for Cellular and Molecular Biology,India)
1992	Swedish Institute Guest Fellowship (Dept of Medical Microbiology and Immunology at Goteborg University with Prof A-M Svennerholm - Peptide Research)
1995	Marie Curie Award, European Union Fellowship (Laboratory of Hospital Infection, PHLS Colindale with Dr TL Pitt-Molecular epidemiology)
2000	Award for Research Invention between the Public and Private Sector, Prime Minister's Department, Malaysia
2000	Silver Medal for Melioidosis Diagnostic Kit International Trade Exhibition (ITEX), Malaysia
2001	Silver Medal for Melioidosis Diagnostic Kit MOSTE Silver Jubilee Exhibition, Malaysia
2001/2002	British Chevening Scholarship - Royal Society Malaysian Fellowship at Imperial College, University of London, UK
2006/2008	FAIMER Institute Fellowship ECFMG, Philadelphia, USA
2008	Australia-Malaysia Institute Fellowship Monash University, Melbourne, Australia

POSTGRADUATE APPOINTMENTS

Sept 1982-Dec 1983	Research Officer, Department of Microbiology, University of Surrey, UK
Feb 1984- Feb 1986	Research Fellow, Department of Tropical Hygiene, London School of Hygiene and Tropical Medicine, UK
Mar 1986-Aug 1986	Seconded on 'field project' in Malaysia, Department of Medical Microbiology, Faculty of Medicine, University of Malaya, Malaysia
Sept 1986-Nov 1986	Research Fellow Department of Microbiology, Faculty of Medicine, University of Malaya, Malaysia
Dec 1987-Dec 1988	Post-doctoral Research Associate Department of Microbiology University of Maryland, MD 20742, USA
Mar 1989 - April 1998	Lecturer, Department of Medical Microbiology, Faculty of Medicine, University of Malaya, Malaysia
May 1998 – Jan 2003	Associate Professor (Reader) Department of Medical Microbiology, Faculty of Medicine, University of Malaya, Malaysia
Feb 2003 – present	Professor Department of Medical Microbiology, Faculty of Medicine, University of Malaya, Malaysia

PAPERS AND PROCEEDINGS OF MEETINGS

1. Lloyd BJ and Vadivelu J (1983). The development and evaluation of a membrane-filter immunoassay for enterotoxigenic *Escherichia coli*. Proceedings of INSERM, 114: 555-581.

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5. Puthucheary SD, Vadivelu J, Phipps M, Parasakthi N (1990). *Aeromonas* septicaemia. 2nd Western Pacific Congress on Infectious Diseases and Chemotherapy. December 11-14, 1990, Thailand.

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implicated bacteria in diarrhoeal diseases. 5th National Biotechnology Seminar, Malaysia.

8. Wong KT, Vadivelu J, Puthucheary SD and Tan KL (1994). In vivo intracellular localization of *Burkholderia pseudomallei* within phagocytes: Histological and ultrastructural evidence. First International Congress of Parasitology and Tropical Medicine. Kuala Lumpur, Malaysia.

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12. Wong KT, Vadivelu J and Puthucheary SD (1994). An immunohistochemical method for the detection of *Burkholderia pseudomallei* infections. International Symposium of Melioidosis, Kuala Lumpur, Malaysia.

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Malaysia. International Congress on Melioidosis, Bangkok, Thailand. **INVITED SPEAKER.**

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24. Vadivelu J (2000). Melioidosis: Approaches in diagnostic procedures, virulence and epidemiology. The 10th Scientific meeting of the Malaysian Society of Molecular Biology and Biotechnology, Kuala Lumpur, Malaysia. **KEYNOTE LECTURE**

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29. Kumutha Malar Vellasamy, Vanitha Mariappan, Jamuna Vadivelu, Onn Hashim (2006). Comparison of secretory protein profile of *Burkholderia pseudomallei* and *Burkholderia thailandensis* using two-dimensional gel electrophoresis. 9th A-IMBN Conference & 16th MSMBB Scientific Meeting, 3rd – 5th September, 2006, Legend Hotel, Kuala Lumpur.

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34. Jeyanthi Suppiah,_Prashanth G. Bagali and Jamunarani Vadivelu (2007). Development of Polymerase Chain Reaction assay to detect *Burkholderia* genus and to differentiate the species in clinical specimens. The 5th World Melioidosis Congress 21st – 23rd November 2007, Khon Kaen, Thailand

35. Eu Lin Chuan, Wong Kum Thong, Jamuna Vadivelu (2007). TUNEL assay suggest evidence of apoptosis in human *Burkholderia pseudomallei* infection. The 12th Biological Sciences Graduate Congress, 19th – 22nd December 2007, University of Malaya

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38. Desa MN, Vadivelu J, Sekaran SD, Parasakthi N (2008). Serotype-specific invasiveness and carriage prevalence in pneumococci in relation to growth pattern *in vitro*. 13th International Congress on Infectious Diseases (ICID) International Scientific Exchange Preliminary Abstract Number: 3127

39. Kumutha MV, Vanitha M, Thimma J, Hashim O, Vadivelu J (2008). Invasion efficiency of *Burkholderia pseudomallei* from different clinical sources. 13th International Congress on Infectious Diseases (ICID) International Scientific Exchange Preliminary Abstract #3470

40. Thimma J, Kumutha MV, Sekaran SD, Vadivelu J (2008). Hyperosmolarity condition enhances *Burkholderia pseudomallei* invasion to epithelial cells. 13th International Congress on Infectious Diseases (ICID) International Scientific Exchange Preliminary Abstract #3482

41. Vanitha M, Kumutha MV, Hashim O, Vadivelu J (2008). Identification of immunoreactive secretory antigens from *Burkholderia cepacia* against monoclonal antibody. 13th International Congress on Infectious Diseases (ICID) International Scientific Exchange Preliminary Abstract #3486.

42. Ramli NSK, Vadivelu J (2008). Biofilm formation of *Burkholderia pseudomallei*.
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pseudomallei from cultures. 13th International Congress on Infectious Diseases
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45. M.V. Kumutha, M. Vanitha, J. Thimma, O. Hashim, J. Vadivelu (2008) Immunoproteomics analysis of *Burkholderia pseudomallei* secretome. The 13th Biological Sciences Graduate Congress 15th -17th December 2008. National University of Singapore.

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51. M.V. Kumutha, M. Vanitha, O. Hashim, J. Vadivelu (2009). Proteome mapping and identification of *Burkholderia pseudomallei* secreted proteins. The 14th Biological Sciences Graduate Congress 10th -12th December 2008. Chulalangkorn University, Thailand.

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53. K. Yalda, S. T. Tay, J. Vadivelu (2009). Prevalence and characterization of ß-lactamases-producing *Pseudomonas aeruginosa* in Malaysia. The 14th Biological Sciences Graduate Congress 10th -12th December 2008. Chulalangkorn University, Thailand.

PUBLICATIONS

1. Vadivelu J, Drasar BS, Cox NP, Lloyd BJ, Feachem RG and Harrison TJ (1987). A membrane-filter assay for the detection of enterotoxigenic *Escherichia coli* in epidemiological studies. *The Lancet* **i**: 1007-9.

2. Vadivelu J, Dunn DT, Feachem RG, Drasar BS, Cox NP, Harrison TJ and Lloyd BJ (1987). Comparison of five assays for the detection of heat-labile enterotoxin of *Escherichia coli*. *J Med Microbiol* **23**:221-6.

3. Vadivelu J (1988). Detection methods for enterotoxigenic *Escherichia coli* in epidemiological studies. PhD thesis. *University of London*.

4. Vadivelu J, Parasakthi N and Puthucheary SD (1988). Detection of heat-labile enterotoxin of *Escherichia coli* by Biken assay and GM1-ELISA. *Singapore Med J* **29**:17-9.

5. Vadivelu J, Feachem RG, Drasar BS, Harrison TJ, Parasakthi N, Thambypillai V and Puthucheary SD (1989). Enterotoxigenic *Escherichia coli* in the domestic environment of a Malaysian village. *Epidemiol Infect* **103**:497-511.

6. Dunn DT, Vadivelu J, Feachem RG, Drasar BS and Cox NP (1989). The value of assay repetition in epidemiological studies. *J Microbiol Methods* **10**:207-14.

7. Vadivelu J, Puthucheary SD and Parasakthi N (1991). Exotoxin profiles of clinical isolates of *Aeromonas hydrophila*. *J Med Microbiol* **35**:363-7.

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9. Surendran Mahalingam, Yuet-Meng Cheong, Spencer Kan, Rohani Md Yassin, Vadivelu J and Tikki Pang (1994). Molecular epidemiologic analysis of *Vibrio cholerae* O1 isolates by pulsed-field electrophoresis. *J Clin Microbiol* **32**: 2975-79.

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macrorestriction analysis of isolates of *Burkholderia pseudomallei* from cases of sporadic melioidosis. *Trans Roy Soc Trop Med & Hyg* **91**:358-360.

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BOOK

Puthucheary SD and Vadivelu J (2002). Human Melioidosis. *Singapore University Press* ISBN 9971-69-261-9

COMMERCIALISATION

- We have identified antigens and developed purification methods, which have now been licensed to PanBio Pty Ltd, Australia. Two tests for melioidosis have been developed, a rapid IgG and IgM immunochromatographic test and ELISA and these will be marketed worldwide. Further discussions are on-going with other commercial companies to use our monoclonal antibodies as diagnostic reagents.

- Monoclonal antibodies for strain identification of B pseudomallei is marketed by AllEights (M) Sdn Bhd

PATENTS

- *Burkholderia pseudomallei* antigen preparation for immunchromatographic assay (Licensing)
- Monoclonal antibody cell lines for detection of *Burkholderia pseudomallei* (Licensing)
- Novel polymerase chain reaction for differentiation and specific detection of *Burkholderia spp* from clinical samples (2008). (PI 20083144).

GENBANK DEPOSITS

Thimma J, Devi S, Vadivelu J (2008)
EU884113 (*Burkholderia pseudomallei* BPSL 1661 gene, partial)

Thimma J, Devi S, Vadivelu J (2009)
FJ820041 (*Burkholderia pseudomallei* LMF clinical isolate partial gene sequence of putative cell surface protein)
FJ820040 (*Burkholderia pseudomallei* LMF clinical isolate partial gene sequence of putative exported protein)
GQ339599 (*Burkholderia pseudomallei* LMF clinical isolate catalse-peroxidase partial sequence)
GQ339600 (*Burkholderia pseudomallei* LMF clinical isolate DNA gyrase subunit A partial sequence)
GQ339601 (*Burkholderia pseudomallei* LMF clinical isolate RNA polymerase sigma E factor partial sequence)

Khosravi Y, Tay ST, Vadivelu J (2009)
GQ221781 (*Pseudomonas aeruginosa* strain Ps-3 metallo-beta-lactamase IMP-7 Gene).
GQ221782 (*Pseudomonas aeruginosa* strain Ps-4 metallo-beta-lactamase IMP-4 Gene).
GQ221780 (*Pseudomonas aeruginosa* strain Ps-2 metallo-beta-lactamase VIM-2 Gene).
GQ221779 (*Pseudomonas aeruginosa* strain Ps-2 metallo-beta-lactamase VIM-11Gene).

Ongoing:

Title: Dissecting the Host-pathogen Enigma: A case for *Burkholderia pseudomallei*
Source of funding: MOSTI (Ministry Special Fund)
Period: 2007-2011

Title: Familial Hypercholesteraemia
Source of funding: MOSTI (Ministry Special Fund)
Period: 2006-2011

Title: Identification of functionally important adhesin protein of *Burkholderia pseudomallei* using siRNA mediated gene silencing
Source of funding: University of Malaya
Period: 2008-2010

Title: Developing adhesin molecules as candidate vaccines using Burkholderia *pseudomallei* as the model organism
Source of funding: University of Malaya
Period: 2009-2012

Title: Development of molecular screening kit for diagnosis and management of diabetes mellitus (Type 2) in Malaysian population.
Source of funding: University of Malaya
Period: 2009-2012

Title: Identification of common immunogenic proteins from *Burkholderia cepacia* secretory proteins
Source of funding: University of Malaya
Period: 2009-1010

Completed

Title: *Vibrio cholerae* - The role of the environment on bacterial survival and virulence
Source of funding: IRPA
Period: 1996-1998

Title: Human Meliodiosis - Pathogenic mechanisms and development of rapid diagnostic procedures
Source of funding: IRPA
Period: 1997-2000

Title: Molecular diagnostic and functional genomics of *Burkholderia* using bioinformatics tools
Source of funding: IRPA
Period: 2005-2007

Title: Identification of adhesion protein of *Burkholderia pseudomallei*
Source of funding: University of Malaya
Period: 2007-2008

Title: Comparison of secreted proteome in clinical and environmental *Burkholderia cepacia* using bioinformatic tools
Source of funding: University of Malaya
Period: 2007-2009

Title: Genotypic characterization and identification of *Pseudomonas aeruginosa* from different clinical conditions
Source of funding: University of Malaya
Period: 2007-2009

Title: Analysis of host cellular response to exposure with *Burkholderia pseudomallei* using microarray
Source of funding: University of Malaya
Period: 2007-2009

Title: Molecular diagnostic and functional genomics of *Burkholderia cepacia* using bioinformatics tools
Source of funding: University of Malaya
Period: 2006-2007

WHAT IS SUCCESS?

Success is to win over your troubles
And have a beautiful smile on your face

Success is to share your precious moments
With needy, helpless, poor & disabled people
hings

Success is to have a sleep with noble thoughts
And wake up with full enthusiasm for your work

Success is to see the beauty in simple & ordinary t
And appreciate them form the heart

Success is to walk without any burden,
And make others feel comfortable in journey

Success is to have patience when things go hard,
And you still believe that you will win at last.

-Pushkar Bisht