



## SingHealth Tissue Repository List of Collections

Title of Project	Principle Investigator	Types of Tissue	Abstract/Summary
A Pilot Study to Investigate Visceral Adipose Tissue in Chinese and Indian men.	Dr Alvin Ng Dept of Endocrinology SGH	Fast venous blood: 1) Plasma 2) Buffy Coat	<a href="#">Click Here</a>
Neuroimmunology Database and Tissue Repository.	Dr Kelvin Tan Dept of Neurology NNI	Whole Blood 1)Serum 2)Plasma 3)Buffy Coat 4)Cerebrospinal Fluid	<a href="#">Click Here</a>
Screening of sera specific IgE to multiple allergen sources (dust mites, insects, indoor and outdoor fungi, tree pollen, weed and grass pollen, plant-, meat-, and dairy/poultry-based foods, seafoods, animal epithelial, venoms and latex) on a miniaturized multi-allergen array and the identification of the major allergens in dust mites using sera of consecutive atopic individuals attending the otolaryngology specialist clinic.	Dept of Otolaryngology SGH	Whole Blood (Serum)	<a href="#">Click Here</a>
The Singapore Prospective Study Program: Lipids, lipoproteins and Coronary Artery Disease risk in Chinese, Malays and Indians. Genes, diet, lifestyle and their interactions in risk determination.	Dr Daniel Wai Dept of Endocrinology SGH	Whole Blood 1)Serum 2)Plasma 3)Buffy Coat	<a href="#">Click Here</a>
Singapore Armed Forces Coronary Atherosclerosis Project (SAFCAP)	Dr Terrance Chua Dept of Cardiology NHC	Venous Blood 1)Plasma 2)Buffy Coat	<a href="#">Click Here</a>
Longitudinal changes of bone mineral density in multiple myeloma – impact on vitamin D status and different treatment regimens	Dr Alvin Ng Dept of Endocrinology SGH	Fast venous blood: 1)Serum 2)Plasma 3)Buffy Coat	<a href="#">Click Here</a>
Novel Biomarkers for Myocardial Infarction based on protein Heterogeneity	A/Prof Lim Swee Han Dept of Emergency Medicine SGH	Whole Blood 1)Plasma 2)Buffy Coat	<a href="#">Click Here</a>



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Title of Project	Principle Investigator	Types of Tissue	Abstract/Summary
Molecular Biology of Central Nervous System (CNS) Tumors	Dr Teo Wan Yee Dept of Paediatric Medicine KKH	1)Whole Blood 2))CSF 3)Brain Tissue 4)Cerebrospinal Fluid	<a href="#">Click Here</a>
The Singapore Lymphoma Study	Prof Teh Bin Tean Division of Medical Sciences NCC	Whole Blood Lymph Node	<a href="#">Click Here</a>

## VI. Abstract of Research Proposal

*In no more than 300 words, describe concisely the specific aims, hypotheses, methodology and approach of the application, indicating where appropriate the application's importance to science or medicine. The abstract must be self-contained so that it can serve as a succinct and accurate description of the application when separated from it. Please use lay terms. If this not possible, the technical and medical terms should be explained in simple language.*

Coronary heart disease (CHD) is the most common cause of sudden unexpected death in adults in Singapore and the second most common cause of death. Conventional screening tests for CHD such as exercise stress testing have limited accuracy and there is increasing interest in the potential of newer non-invasive tests such as calcium scoring and carotid intima-media thickening for the early detection of atherosclerosis. However there is limited data on the prevalence of elevated calcium scores, carotid intima-media thickening and their relationship to traditional risk scores and stress testing in our local population.

This study seeks to a) compare the prevalence and relationship of atherosclerosis burden as assessed by these non-invasive tests and the Framingham risk score in asymptomatic men from 3 main ethnic groups in Singapore and b) assess their potential value in the screening of men for atherosclerosis prior to fitness testing and military training. Asymptomatic men aged 40 and above undergoing routine screening prior to annual fitness tests will be offered calcium scoring, carotid intima-media measurement, high sensitivity CRP and ankle-brachial index measurement, in addition to the current standard exercise test, lipid and blood sugar measurement, history and physical examination. The prevalence and distribution of calcium scores, carotid intima-media thickening and abnormal stress tests will be compared across different ethnic groups. It is hypothesized that the prevalence of elevated calcium scores and carotid intima-media thickening will differ with ethnic group. The proportion of patients with negative stress tests but elevated calcium, and abnormal stress tests with no calcium will be examined to determine the relationship between calcium and stress testing in an asymptomatic population. The relationship between carotid intima-media thickening and calcium scores will also be examined. Patients with elevated calcium score or abnormal stress tests will be referred for stress myocardial perfusion imaging, which will be used as the "gold standard" for detection of myocardial ischaemia. The study will help to determine if calcium scoring has a role in the screening of men prior to military fitness testing, for example as a test to be performed if the treadmill ECG stress test is abnormal, prior to nuclear perfusion imaging. This study will subsequently form the basis for a long term cohort study evaluating the relative prognostic value of Framingham risk scores and non-invasive tests in Singaporeans.

## **Abstract**

**Screening of sera specific IgE to multiple allergen sources (dust mites, insects, indoor and outdoor fungi, tree pollen, weed and grass pollen, plant-, meat-, and dairy/poultry-based foods, seafoods, animal epithelial, venoms and latex) on a miniaturised multi-allergen array and the identification of the major allergens in dust mites using sera of consecutive atopic individuals attending the otolaryngology specialist clinic**

**Keywords: Allergy, Rhinitis, Atopy**

**We are proposing for screening of specific IgE to multiple allergen sources in patients diagnosed with allergic rhinitis. The project will be done in collaboration with the Department of Biological Sciences, NUS. The aim of the project is to identify the major source of allergens (dust mites, insects, indoor and outdoor fungi, tree pollen, weed and grass pollen, plant-, meat-, and dairy/poultry-based foods, seafoods, animal epithelial, venoms and latex) triggering allergic symptoms on consecutive atopic individuals attending the otolaryngology specialist clinics, identify the major allergens in dust mites using the same set of consecutive sera and screened on a dust mite recombinant allergen array containing the majority of the cloned allergens from house dust mites, to correlate the array screening data with data obtained from the existing clinical laboratory tests, as well as to understand and predict the degree of cross and co-sensitization to multiple allergen sources, and to evaluate the predictive value of the test results with clinical data and outcomes of therapeutic and avoidance measures.**

**We will be using a miniaturised multi-allergen array with 150 different types of allergens. The advantages of this study is which 1) does not expose patients to allergens, 2) enables simultaneous testing of a large panel of allergens in a short time, 3) has a minimal cost, and 4) at the same time use very little or minimal samples.**

## **VI. Abstract of Research Proposal**

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### **Background:**

Multiple sclerosis (MS) is an uncommon disease in Singapore. In Asia, MS appears to have different disease characteristics and may respond to treatments differently compared to the western population. Locally, there are many autoimmune diseases which can mimic MS phenotypically, complicating diagnosis and therapy. It is a disease affecting young patients in their prime but its etiology is still not well understood and treatments not completely effective.

### **Objectives:**

To establish a large repository of DNA, blood cells, plasma, serum and CSF of patients with neuroimmunological conditions such as Multiple Sclerosis and other autoimmune disease which causes central nervous system (CNS) demyelination with an accurate, well-characterized clinical database.

### **Methods:**

**Study Design:** Prospective Database and DNA, blood and CSF repository.

All inpatients and outpatients presenting to the National Neuroscience Institute (TTSH campus) or Ophthalmology department, TTSH for CNS demyelinating disease or optic neuritis and have consented to participate in the study will be eligible for inclusion. After obtaining informed consent from the patient and permission from the primary physician, data on demographics, family history and pedigree that includes gender and age of relatives up to the second degree, current medications, and results of routine and specialized blood tests and CSF analysis, neuroradiological and electrophysiological (evoked response) examinations will be collected through interview and review of case notes.

Blood and CSF samples will be collected for storage and extraction of DNA material, blood cells, plasma and serum.

### **Significance:**

A DNA, blood and CSF specimen repository linked to a comprehensive database of consistent and accurate clinical and neuroradiological information of patients with Multiple Sclerosis and other autoimmune disease which causes central nervous system (CNS) demyelination, will permit multiple epidemiological, genetic, and biological studies that will help us understand the etiology, pathogenesis and potential diagnostic and therapeutic strategies for these diseases.

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The metabolic syndrome is a major public-health challenge worldwide as it leads to increased risk of cardiovascular disease. Central obesity, hypertension, raised triglycerides, reduced HDL-cholesterol and raised fasting glucose are its components. Its prevalence in Singapore is 17.9% overall but 31% at the age group of 60-69. Thus it will become more and more important. Central obesity has been defined by the International Diabetes Federation (IDF) to be its essential factor due to its role in the basic pathophysiology of the disorder. Central obesity is approximated by measuring the waist circumference. It has been suggested that the criteria for the definition of central obesity developed for one population may not be applicable to other populations. On this basis, the IDF and the American Heart Association (AHA) have both made recommendations that lower cut-offs should be used to define central obesity in individuals from Asian ethnic groups.

Unfortunately, few of these recommendations have been based on examination of the actual relationship between waist circumference and an assessment of visceral adipose tissue (VAT) mass (which is the biologically active component of central obesity). The only country that has done this in Asia has been Japan and on the basis of their assessments, they use different definitions of central obesity compared to those recommended for Chinese and Indians by the IDF and the AHA. Emerging data comparing Caucasians and Asians suggest that the correlation between waist circumference and visceral adipose tissue mass differs between ethnic groups. As such, to validate the recommendations in our population, it is important that we explore in Chinese and Indian men: 1) the relationship between waist circumference and visceral adipose tissue mass; 2) the relationship between visceral adipose tissue mass and features of the metabolic syndrome; and 3) the possibility that other biomarkers may serve as better measures of visceral adipose tissue mass than the waist circumference that could be useful in both populations.

Coronary calcium predicts cardiovascular disease. VAT had been shown to be correlated to coronary calcium in Caucasian men but not women. There is paucity of data in Asians and it is therefore important to explore the correlation between VAT and coronary calcium, especially given that Indians have higher incidence of coronary heart disease.

Apart from its effects on the cardiovascular disease, there is increasing evidence of obesity having a negative effect on bone health. Traditionally, it is well recognised that BMI has positive correlation with bone mass. However, when the effects of mechanical loading due to body weight has been accounted for, obesity has been shown to be a risk factor for osteoporosis. Most previous studies have measured total fat mass in relation to bone mass. There is limited data (and none in our population) on the relation between specific compartments of adipose tissue (such as visceral vs subcutaneous) on bone mass.

120 patients will be recruited consisting of 60 Chinese men and 60 Indian men. Medical history will be taken. Height, weight, blood pressure, and waist circumference will be measured. Fasting glucose, insulin, lipids, adipokines, calcium, 25-hydroxy vitamin D, bone turnover markers and inflammatory marker levels will be measured. Multi-slice CT and Dual Energy X-ray Absorptiometry (DXA) scan will be done. Coronary calcium, bone

mineral density and VAT volume will be measured. We will compare 1) the correlations between visceral adipose tissue mass and the waist circumference in Chinese and Indian men to determine the level of waist circumference that gives the same volume of VAT; 2) the correlations between VAT volume and insulin resistance, plasma lipids, plasma glucose, blood pressure and coronary calcium to determine whether VAT volume has the same metabolic effects in Chinese and Indian men; 3) other markers (adipokines, inflammatory markers) against the waist circumference as a marker for VAT volume in Chinese and Indian men in order to derive a predictive model for assessing VAT volume without the requirement for CT scan and 4) the correlations between VAT volume, 25-hydroxy vitamin D level, bone turnover markers and bone mineral density.

This project will allow us to make rational recommendations with regards appropriate definitions of central obesity in our populations based on scientific data. The identification of biomarkers that better define central obesity could give rise to clinical tools that allow more precise estimates of central obesity in the clinical setting. Finally, the study will also allow us to study the relationship between central obesity, coronary calcification and bone strength.

**Title: Novel biomarkers for myocardial infarction based on protein heterogeneity**

**Abstract**

The diagnosis of non-ST elevation myocardial infarction (NSTEMI) can be missed or delayed resulting in increased morbidity and mortality. To avoid this, many patients are admitted unnecessarily to exclude myocardial infarction. Biomarkers could facilitate early diagnosis and triage patients to receive intensive anti-thrombotic or revascularization therapy and reduce the cost of hospitalization and investigations. Proteins exist in the plasma as multiple variants, each of which may have different diagnostic utility and which cannot be detected using conventional immunoassay approaches (ELISA and RIA). Using mass spectrometric immunoassay (MSIA), our collaborators have identified variants of transthyretin, serum amyloid A, and creatine kinase which appear to differentiate effectively between patients with and without myocardial infarction. However, the time course of any changes in the levels of these biomarkers following myocardial infarction and their ability to discriminate between those with and without myocardial infarction are unknown. We will carry out a nested case-control study (88 cases with major adverse cardiovascular events and 88 controls). They will be selected from a cohort of 1500 patients who undergo observation in emergency department for chest pain or symptoms possibly due to acute coronary syndrome, without the classical ECG changes of ST elevation myocardial infarction (STEMI) or ST depression of NSTEMI, who will be followed up for 30 days. The concentrations of S-sulfonated TTR, serum amyloid A 1 $\alpha$ , myoglobin and novel variants of the M and B isoforms of creatine kinase will be measured at 0, 2 and 7 hours. Changes in the levels of these protein variants following the onset of chest pain will be compared between cases and controls. The ability of these novel variants to discriminate between cases and controls will be compared with a known biomarker (troponin T). If successful, this could give rise to novel diagnostic tests that could be used in the ED.

*Principle Investigator: Dr TEO WAN YEE (Acting PI: A/Prof Tan Ah Moy)*

**PROJECT: Molecular Biology of Central Nervous System (CNS) Tumors**

**SUMMARY OF RESEARCH PROJECT**

Central nervous system (CNS) tumors are the second most common malignancy of childhood, making up approximately 20% of all pediatric cancers.<sup>1</sup> CNS tumors are the leading cause of cancer-related death in childhood.<sup>2</sup> Although significant progress has been made in the treatment of certain childhood CNS tumors, such as non-disseminated medulloblastoma and low grade glioma, there is still a great need to improve survival for high risk tumors, and reduce long-term neuropsychological/neuroendocrine deficits related to tumor or treatment. There is an urgent need to identify new prognostic markers to stratify patients to risk-based therapies. Increasing use of molecular tools to study pediatric brain tumors has led to the recognition that broad groups of histologically similar lesions may actually encompass distinct subgroups that exhibit vastly different prognoses. This translates into an urgent need for pediatric brain tumor tissue banking in Singapore. With the advent of high- throughput genomic technologies, it is now possible to generate comprehensive molecular profiles of tumors through using small quantities of tissues that are available through brain tumor tissue banking.

Genomic profiling will aid in our understanding of pathogenesis of pediatric brain tumors and refine treatment. These clinically relevant profiles must be validated with independent data sets by multiple institutions; studies in progress are currently within the Children's Oncology Group. Molecular profiling will provide important clues regarding critical pathways that tumor cells are dependent on to maintain their malignant phenotype which are ideal therapeutic targets for tumor-specific therapies. Molecular profiling will also aid in decreasing the intensity of neurotoxic therapies to reduce the morbidity of treatment in tumors that have particularly favorable risk factors as determined by genomic profiling.<sup>3</sup>

## **SINGAPORE LYMPHOMA STUDY**

### **Summary of Research Project**

Currently, epidemiology and clinical data on lymphoid neoplasms is derived mainly from Western series. An increasing body of information from our center and other suggest that geographic localities as well as ethnicity are important factors and extrapolation of experience and data from the West to the Asian setting may have limitations. More importantly, the detailed clinical and molecular data obtained from this study will form the basis of all future research and healthcare planning.

The main purpose of this proposal is:

- a. To exhaustively evaluate the molecular characteristics of lymphoma, particular subtypes that occur at higher frequencies in Asians.
- b. To develop new biomarkers, diagnostic assays, treatment targets and novel treatment strategies, particularly against lymphoma subtypes unique to Asians.

Official No:

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**6. PROPOSED START AND END DATES**

Please allow at least 4 months for the review process.

Start (Mth/Year): Jan 2003End (Mth/Year): Dec 2005**7. SUMMARY OF PROPOSAL**

In no more than 300 words, please provide a brief description of the proposal, the rationale, its distinguishing features and how the research can advance knowledge and understanding in the relevant field of research.

Plasma lipoproteins concentrations are major modifiable risk factors for coronary heart disease (CHD). We hope to capitalise on 3 unique aspects of Singapore in this proposal. 1) The population comprises 3 ethnic groups of differing genetic background (our preliminary studies have shown that the frequencies of genetic variants in key candidate genes involved in lipoprotein metabolism differ between ethnic groups). 2) we have shown that rapid socio-economic development in Singapore has affected each ethnic group differently. Asians Indians have three time greater risk of CHD and higher levels of risk factors including diabetes mellitus, insulin resistance and low HDL cholesterol. 3) the Singapore government has conducted two National Health Surveys providing a 5-10 year head-start on other investigators.

We propose the recall of subjects studied in the 1998 National health survey (n=4723) to collect additional information on clinical, biochemical, dietary and genetic parameters. Using these data, we will examine the role of plasma lipoproteins and their subfractions in the pathogenesis of CHD in Singapore. We will also examine the role of genetic variants and environmental/lifestyle factors, as well as any gene-environment interactions present that may alter lipid and lipoprotein concentrations in all three ethnic groups. Finally, we will re-calibrate the Framingham CHD predictive function for use in Asian populations.

Our proposal marks the first step in the development of personalised lifestyle changes based on genotype and phenotype that are culturally and ethnically sensitive for Asia. Potential applications include the primary prevention of CHD in Asia and the development of functional foods for the Asian market that modulate lipoprotein levels. We plan to archive biological samples (serum/plasma/DNA) to create a bank that will allow other investigators in Singapore to carry out studies in other areas including diabetes mellitus and hypertension. Singapore is uniquely placed to unravel the contributions of nature versus nurture in the pathogenesis of these chronic diseases and stands to become a reference centre for the region.

## 12 DETAILS OF RESEARCH PROPOSAL (Maximum: 25 pages)

### ABSTRACT OF PROPOSAL (not more than 300 words)

(Provide a summary of the project: its objectives, methodology, major accomplishments and other relevant information.)

Skeletal complications are a major cause of morbidity in multiple myeloma (MM). These complications include hypercalcemia due to increased bone resorption, generalized bone loss, intractable bone pain due to lytic bone destruction, and pathologic fractures at skeletal sites compromised by osteolytic lesions (1, 2). Vitamin D is a fundamental mediator of skeletal metabolism. In addition, it has numerous non-skeletal actions of importance, including the regulation of cellular proliferation, differentiation, apoptosis, and angiogenesis. Therefore vitamin D deficiency may be an important contributor to the spectrum of skeletal complications seen in MM and an important determinant of the progression and prognosis of MM. In-vitro studies demonstrating the anti-proliferative and pro-apoptotic effects of 1,25(OH)<sub>2</sub>D<sub>3</sub> analogs in myeloma cell lines (3-6) support this hypothesis. However, human studies on the relationship between vitamin D deficiency and MM are notably lacking. The need for such studies is even more urgent considering the current "pandemic" of vitamin D deficiency. Using more recently recommended cut-offs for serum 25 hydroxyvitamin D [25(OH) Vit D] levels, recent studies have reported that a high proportion of community-dwelling men and women in both tropical and temperate climates are deficient in vitamin D (7).

Our central hypotheses are that in the MM population, 1) vitamin D deficiency is prevalent 2) that increased vitamin D deficiency may be associated with worsened skeletal disease, and 3) that vitamin D may play a role in the progress and prognosis of the disease itself.

Therefore, the specific aims of our study are :

1. Determine the prevalence of vitamin D deficiency in our MM population
2. Determine changes in bone mineral densities (BMD) in MM in a longitudinal fashion
3. Correlate the vitamin D status to BMD and other outcomes including progression of disease, development of skeletal-related events and quality of life.