**LKCMedicine PhD Research Project Submission Form**

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<th>Research Theme (Please indicate as appropriate)</th>
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**Research Project Title:**

Can intensive lifestyle modification prevent type-2 diabetes in high risk normoglycaemic individuals?

**Project Description:**

**Background**

Type-2 diabetes (T2D) is a major public health problem, driven by a global epidemic of overweight and obesity. Although genetic factors are recognised to contribute to T2D, the current epidemic of diabetes emphasises the importance of environmental and lifestyle factors as major determinants of T2D.

A rigorous programme comprising intensive lifestyle modification in overweight and obese people with impaired glucose tolerance had been shown to be clinically beneficial, with almost 50% relative risk reduction in the incidence of T2D. However, whether the clinical benefits are also extended to high risk normoglycaemic individuals is still not clinically proven. Completing a randomized trial is the only approach to address this question.

**Aims**

Specifically, this project aims to:

1. Identify 1,500 normoglycaemic individuals predicted to be at high risk of T2D (>10% per annum), using a validated calculator developed in the laboratory.
2. Design and complete a randomized clinical trial to determine if
   i. Intensive lifestyle modification and
   ii. Pharmacological intervention reduce risk of T2D, compared to usual care, amongst the 1,500 people predicted to be at high risk of T2D based on molecular risk score.

**Approach**

Singapore Chinese men and women aged 35-75 years will be screened to identify 1,500 individuals who are normoglycaemic but predicted to be at high risk of T2D (≥10% per annum) based on their molecular risk score. Potential participants will be identified from a population study (Health for Life in Singapore (HELIOS)) of 10,000 Singapore residents. The study participants will undergo a systematic, structured assessment of cardiovascular and metabolic health, including clinical...
questionnaire, anthropometry, non-invasive assessment of cardiovascular performance (ECG, treadmill test, arterial compliance), imaging (retinal and iDEXA), as well as biochemical screening (including glucose, insulin, CRP and HbA1c). Aliquots of plasma, serum and DNA will be stored at -70°C for future molecular epidemiological studies. Individuals meeting the study criteria for the randomized control trial (RCT) will be invited to attend an enrolment visit for potential participation in the RCT.

The randomised clinical trial will compare the outcome amongst the high-risk Singapore Chinese men and women identified from the above screening and randomized into the following pathways for preventing T2D i. intensive lifestyle modification (N=300), or ii. pharmacologic intervention (Metformin, N=600) vs usual medical care (single session of lifestyle advice, N=600). The asymmetric sample size between lifestyle and pharmacologic intervention is an efficient design, reflecting the greater predicted effect size of lifestyle intervention for prevention of T2D. Intensive lifestyle modification will follow clinically accepted, evidence based strategies derived from the Diabetes Prevention Program, to achieve >7% weight reduction through improved diet and increased physical activity, and will be delivered through a combination of face-face, group, telephone and internet based interactions over 12 months. Pharmacological intervention will be with Metformin (initially 500mg od, titrated to 850mg bd if tolerated). Participants will be followed every 12 months for at least three years to identify new onset of T2D.

The clinical trial data will be analysed to quantify absolute reduction in risk of T2D with lifestyle modification or Metformin vs usual care amongst the study subjects. Data will be analysed on an intention to treat basis. Mechanistic substudies will be designed to explore potential relationships between DNA methylation in blood, pancreatic beta cell function and insulin mediated glucose disposal by muscle and other tissues, and the impact of lifestyle modification.

**Brief summary of main Methodologies and/or Techniques to be learned during the proposed PhD (experimental or analytical):**

1. Validation of molecular risk scores ('calculator').
2. Understanding of patterns, causes, and effects of health and disease conditions in diabetes.
3. Design and statistical analyses for clinical trial.
4. Clinical trial management.

**Keywords:** metabolic disease, metabolic disturbance, type-2-diabetes (T2D), epigenome, randomized control trial
**Supervisor(s)**

**Primary Supervisor**

Name of Supervisor: Prof John Chambers  
Designation: Professor of Cardiovascular Epidemiology  
Email: john.chambers@ntu.edu.sg

**Co-Supervisor (need not be determined at this time)**

Name of Supervisor: __________________________  
Designation: __________________________  
Email: __________________________

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**Main Location of Research Work** (Please indicate as appropriate)

- [ ] LKCMedicine Experimental Medicine Building @ Yunnan Campus
- ✗ LKCMedicine Clinical Sciences Building @ Novena Campus

Others (Please specify): __________________________

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**Other Information**

1. Does the proposal need IRB’s approval?  
   - ✗ Yes  
   - [ ] No

   If “Yes”, is the IRB’s approval in place?  
   - [ ] Yes  
   - ✗ No

2. Does the project involve the use of animals?  
   - [ ] Yes  
   - ✗ No

3. Does the project involve contact with patients?  
   - [ ] Yes  
   - ✗ No

4. Is there a potential for overseas academic exchange as part of this research project?  
   - [ ] Yes  
   - ✗ No

   If “Yes”, please specify: __________________________