# LKCMedicine PhD Research Project Submission Form

## Research Theme (Please indicate as appropriate)

- [ ] Dermatology & Skin Biology
- [ ] Health Systems & Population Health
- [ ] Metabolic Disorders
- [ ] Medical Education
- [x] Infection & Immunity
- [ ] Family Medicine & Primary Care
- [ ] Neuroscience & Mental Health
- [ ] Others (Please specify):

## Research Project Title:

Role of “Ionic Checkpoint” in the Regulation of Immune Cell Functions

## Project Description:

Tumour microenvironment interferes with immune surveillance and promotes escape of malignant cells from the host immune system. Immune checkpoint inhibitors (e.g. anti-CTLA4, anti-PDL1) that target regulatory pathways in T cells and enhance anti-tumour immune responses have demonstrated promising efficacy in cancer. But a significant proportion of patients showed resistance to these drugs and severe toxicity. Treatments using immune checkpoint inhibitors cost about $1 million/patient. Recently, “ionic checkpoint” with high levels of extracellular K⁺ ([K⁺]ₑ) in the tumour microenvironment has been identified as a key modulator of T cell functions (Eil et al., 2016, *Nature*). This checkpoint is of fundamental physiological importance since K⁺ is the most abundant exchangeable cation within living cells. However, there are a number of questions remain to be answered, which would open the door to translational research for enhancing anti-tumour activity of lymphocytes and improving immunotherapeutic outcomes. In this project, the student will address the following three aims:-

In **Aim 1**, the student will determine whether the K⁺ checkpoint affects T cells and other immune cells (e.g. monocytes, B cells, NK cells and neutrophils) identically. He/she will ascertain whether blockade of K⁺ efflux from immune cells promotes intracellular accumulation of K⁺ and accelerates the K⁺ checkpoint.

In **Aim 2**, the student will investigate specific signalling and metabolic pathways that are affected by the K⁺ checkpoint in T cells and/or other immune cell types.
In **Aim 3**, the student will evaluate pharmacological strategies to rescue immune cells from K⁺ checkpoint-mediated suppression by enhancing K⁺ efflux.

These studies will represent a significant scientific advancement and offer an improved therapeutic approach for boosting anti-tumour immune responses and minimizing the risk of cancer relapse with broader clinical implications.

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

The student will gain specialized training in immune cell biology, onco-immunology, cell and metabolic signalling, with techniques to include cell culture, microscopy, *in vivo* mouse model for anti-tumour immune responses, cellular, molecular, biochemical and imaging assays. The work presented in the PhD thesis will form the basis of scientific papers to be written by the student.

**Keywords:**
Immunology, cell biology, onco-immunology, anti-tumour immune response, T cell functions.
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<th><strong>Supervisor(s)</strong></th>
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<tr>
<td><strong>Primary Supervisor</strong></td>
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<tr>
<td>Name of Supervisor: Navin Kumar Verma</td>
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<tr>
<td>Designation: Assistant Professor of Immunology and Cell Biology</td>
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<tr>
<td>Email: <a href="mailto:nkverma@ntu.edu.sg">nkverma@ntu.edu.sg</a></td>
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<tr>
<th><strong>Co-Supervisor (need not be determined at this time)</strong></th>
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<tbody>
<tr>
<td>Name of Supervisor: Professor George Chandy</td>
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<tr>
<td>Designation: Professor of Molecular Physiology</td>
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<tr>
<td>Email: <a href="mailto:gchandy@ntu.edu.sg">gchandy@ntu.edu.sg</a></td>
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<tr>
<th><strong>Main Location of Research Work (Please indicate as appropriate)</strong></th>
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<tbody>
<tr>
<td>☒ LKCMedicine Experimental Medicine Building @ Yunnan Campus</td>
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<tr>
<td>☒ LKCMedicine Clinical Sciences Building @ Novena Campus</td>
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<td>Others (Please specify):</td>
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<th><strong>Other Information</strong></th>
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<td>1. Does the proposal need IRB’s approval? ☒ Yes ☐ No</td>
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<td>If “Yes”, is the IRB’s approval in place? ☒ Yes ☐ No</td>
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<td>2. Does the project involve contact with patients? ☐ Yes ☒ No</td>
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<td>3. Is there a potential for overseas academic exchange as part of this research project? ☐ Yes ☒ No</td>
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<td>If “Yes”, please specify: To be determined later</td>
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