Research Theme (Please indicate as appropriate)

☐ Dermatology & Skin Biology  ☐ Family Medicine & Primary Care
☐ Health Systems & Population Health  ☐ Infection & Immunity
☐ Metabolic Disorders  ☐ Neuroscience & Mental Health
☐ Medical Education  ☒ Others (Please specify):
  ☒ stem cell and metabolism

Research Project Title:
Constructing renal cell carcinoma using human PSC-derived kidney organoid model.

Project Description:
Renal cell carcinoma (RCC) accounts for 2% of all cancers, and is characterized by a lack of early-warning signs, diverse clinical manifestations, and resistance to radiotherapy and chemotherapy. The prevalence of end-stage renal disease (ESRD), a consequence of many conditions including genetic defects, diabetes, cancers, cardiovascular diseases, and hypertension, is increasing at an alarming rate. It is important to note that the relationship between RCC and ESRD is bidirectional. Patients with ESRD have 100-fold increased risk for developing RCC. According to the 2016 annual report of National Kidney Foundation, Singapore has world’s 4th highest incidence of kidney failure, in line with the rising incidence of RCC (an annual increasing rate of 2-3%). In spite of the increase of incidence, RCC is a disease that is under-recognized and under-studied, requiring development of effective clinical intervention.

Our understanding of the molecular genetics of RCC has significantly improved in recent years ascribing to the availability of high-resolution Next-Generation Sequencing (NGS). Genetic alterations of a few pathways have been repetitively identified in human RCC patient samples, including cellular oxygen-sensing pathway, chromatin modification pathway, nucleosome remodeling complex, mTOR pathway, p53 pathway, oxidative stress pathway, and Hippo pathway. Despite the fact that proximal tubular epithelial cells are well-identified origin of RCC, it is a mystery how exactly these cells are transformed to become tumour-initiating cells. Isolation of human proximal tubular epithelial cells remains restricted to kidney biopsies obtained from patients with pathological conditions or post-mortem. Traditional 2-Dimensional (2D) monolayer culture of proximal tubular epithelial cells largely deprived the cells from forming their functional tubular structure, thus diverting their cellular properties away from the in vivo counterpart. Moreover, due to the heterogeneity of genetic composition of RCC, transgenic mouse model studies failed to provide a comprehensive disease presentation reminiscent of human RCC. There is an urgent need to establish a reliable platform to model RCC tumour initiation, which will ultimately lead to personalised disease prevention and management.

Based on our preliminary data, we hypothesize that the use of human induced pluripotent stem cells (iPSCs), and their derivatives, in which defined genetic alterations related to cancer are introduced might represent a suitable strategy for the establishment of human cancer model. Patient-specific iPSC-based in vitro differentiation strategies hold the potential to generate controllable platforms to study developmental processes and physiological mechanisms underlying the manifestation of disease phenotypes. Our lab has established a highly efficient differentiation platform to generate 3-Dimensional kidney organoids from human iPSCs. Stem cell-derived kidney organoid platforms can in turn enable the identification and validation of strategies against the manifestation and progression of human kidney diseases. We envision two possibilities for the success of
this approach: 1) that direct differentiation of human iPSCs generates 3D kidney organoids representing *in vitro* platform for both basic research and clinical application; 2) that introduction of relevant genetic alterations transforms human iPSC-derived proximal tubular epithelial cells into RCC tumour-initiating cells (RTICs), which faithfully preserves the genetic background of the parental iPSC line. The accomplishment of this project will greatly advance our understanding of the underpinning mechanisms of RCC initiation, providing amenable platform for future drug validation.

<table>
<thead>
<tr>
<th>Brief summary of main Methodologies and/or Techniques to be learned during the proposed PhD (experimental or analytical):</th>
</tr>
</thead>
<tbody>
<tr>
<td>This project will employ a large variety of up-to-date technologies, including human pluripotent stem cell culture and organoid differentiation, high-resolution mass spectrometry-based metabolomics, genetic modification involving CRISPR/Cas9 tools, microscope imaging, mouse models, and etc.</td>
</tr>
</tbody>
</table>

**Keywords:** human pluripotent stem cell, kidney organoid, differentiation, cancer stem cell, metabolism,
## Supervisor(s)

### Primary Supervisor

<table>
<thead>
<tr>
<th>Name of Supervisor:</th>
<th>Xia Yun</th>
</tr>
</thead>
<tbody>
<tr>
<td>Designation:</td>
<td>Nanyang Assistant Professor</td>
</tr>
<tr>
<td>Email:</td>
<td><a href="mailto:yunxia@ntu.edu.sg">yunxia@ntu.edu.sg</a></td>
</tr>
</tbody>
</table>

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

| Name of Supervisor: | |
|---------------------| |
| Designation:        | |
| Email:              | |

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

- [x] LKCMedicine Clinical Sciences Building @ Novena Campus
- [ ] LKCMedicine Experimental Medicine Building @ Yunnan Campus
- [ ] Others (Please specify): ________________

## Other Information

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

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

2. Does the project involve contact with patients?  
   - [ ] Yes  
   - [x] No

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

   If “Yes”, please specify: ________________