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): System biology and cancer metastasis.

Research Project Title:
Dynamic regulome and interactome of cancer EMT.

Project Description:

Medical Significance. Metastasis is responsible for most of cancer-related death. Cancer-related deaths have not rocketed because of significant advances in diagnosis. However, we have made less progress when it comes to treatment methods. Whereas surgical resection and adjuvant therapy can cure well-confined primary tumors, metastatic cancer is largely incurable because of its systemic nature and the resistance of disseminated tumor cells to existing therapeutic agents. This explains why >90% of mortality from cancer is attributable to metastases, not the primary tumors from which these malignant lesions arise. Thus, our ability to effectively treat cancer is largely dependent on our capacity to interdict - and perhaps even reverse - the process of metastasis. These clinical realities have been appreciated for decades, yet our understanding of this process is limited and there are very few therapeutic options.

Tumor EMT is a graded series of interrelated and overlapping events. Tumor epithelial-to-mesenchymal transition (EMT) is a complex series of cellular reprogramming events that culminates in the loss of epithelial characteristics and the de novo acquisition of a mesenchymal phenotype. The clinical significance of the EMT process is linked to its crucial role in tumor cell invasion, circulating tumour cell formation and metastatic dissemination of carcinomas. Tumor EMT is not an on/off binary switch, but rather a graded series of interrelated and overlapping events that can be quite variable. The process of EMT is now recognized to involve interplay between several different levels of regulation. While many structural proteins represent the characteristic “marker profile” of EMT, the expression of these molecules is mediated by additional layers of control that include regulators that shape the transcriptome and interactome landscapes of cancer cells during EMT.

Background: Using experimental and clinical metastatic tumors, we showed that ANGPTL4 is a novel molecular regulator of EMT-enriched metabolic changes that is required for metastasis competency. A key mechanistic insight is that ANGPTL4 elevates the expression of YWHAG which contributes to an important new signalling axis that coordinates multiple biological processes for metastasis. A high YWHAG expression is a common feature in many tumor types. Analysis of cohort studies showed that high YWHAG expression associated with poor prognosis. YWHAG has significant influence on the transcriptome and cancer cells behavior during EMT via protein-protein interactions. Despite its pivotal
position, little is known about the interactome of YWHAG in cancer cells during EMT, and how these YWHAG-protein interactions enhance metastasis.

**Aims:** We will extend this work and further explicate these observations at a global level by leveraging on our established in vitro cancer EMT models to elucidate the transcriptome of EMT-associated genes modulated through YWHAG interactions ( Aim 1) and to unravel YWHAG interactome that affects cellular processes ( Aim 2).

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

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<th>Animal model:</th>
<th>Dual inducible model for cancer metastasis.</th>
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<td>Cell biology:</td>
<td>In vitro models of cancer EMT, histology, immunohistochemistry, flow cytometry.</td>
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<td>Molecular biology:</td>
<td>Western blot; RNA-seq, Chip-seq and data analysis.</td>
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<td>Proteomics:</td>
<td>PCT-SWATH (pressure-cycling technology coupled with SWATH mass spectrometry)</td>
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**Keywords:** Metastasis, epithelial-mesenchymal transition, interactome.
### Supervisor(s)

#### Primary Supervisor

<table>
<thead>
<tr>
<th>Name of Supervisor:</th>
<th>Andrew Tan Nguan Soon</th>
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</thead>
<tbody>
<tr>
<td>Designation:</td>
<td>Associate Professor (tenured)</td>
</tr>
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<td>Email:</td>
<td><a href="mailto:nstan@ntu.edu.sg">nstan@ntu.edu.sg</a></td>
</tr>
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#### Co-Supervisor *(need not be determined at this time)*

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<th>Name of Supervisor:</th>
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### Main Location of Research Work *(Please indicate as appropriate)*

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

Others *(Please specify)*: ____________________________

### Other Information

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

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

   If “Yes”, please specify: Dr Guo Tiannan *(http://www.guomics.com/)*

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