### Background

- MTL-CEBPA is currently in Phase Ib clinical trials in patients with advanced hepatocellular carcinoma (HCC) (Clinical trial information: NCT02176102).
- MTL-CEBPA comprises a small activating RNA (saRNA) encapsulated inside a SMARTICLES® liposomal nanoparticle to activate CEBPA expression in cells.
- Our preclinical studies have demonstrated that MTL-CEBPA modulates the properties of immune cells in the tumor microenvironment in syngeneic mouse tumour models, improves liver function and suppresses tumor growth in tumour models in immunocompetent mice and rats.
- Administration of MTL-CEBPA to patients increases the CEBPA mRNA expression in circulating white blood cells.
- However, the cell types targeted by MTL-CEBPA in the immune system are not well defined.

### Aim

- The aim of the study is to extend our knowledge on the biodistribution of MTL-CEBPA to cells of the immune system.

### RNA activation mechanism

1. Loading of saRNAs into Ago2 protein
2. saRNA-Ago complex enters nucleus and associates with promoter region of target gene
3. Generation of a transcriptional activation complex to generate new mRNA
4. Synthesis of new protein

### MTL-CEBPA Drug Product

- **CEBPA-s1** saRNA to upregulate CEBPA expression
- **NOV340** SMARTICLES® liposome
- **MTL-CEBPA** Formulation
- **MTL-CEBPA** Drug Product

### Flow cytometry gating strategy

- **T cells**
  - **B cells**
  - **Monocytes**
  - **Macrophages**
  - **Dendritic cells**
  - **Neutrophils**

### MTL-Cy3-CEBPA uptake in CD34+ cells

- **CD34+ cells**
  - The CD34+ cells in bone marrow but not in blood uptake MTL-Cy3-CEBPA.

- **Blood, bone marrow and spleen were harvested post**
  - **MTL-CEBPA was intravenously injected in Wistar rats.**

### MTL-Cy3-CEBPA uptake in myeloid cells

- **Monocytes**
  - The monocyte populations in blood, bone marrow and spleen mediate a significant uptake of MTL-Cy3-CEBPA.

- **Macrophages**
  - The macrophage populations in blood and spleen, but not in bone marrow mediate a significant uptake of MTL-Cy3-CEBPA.

- **Dendritic cells**
  - The dendritic cell populations in blood and bone marrow mediate a significant uptake of MTL-Cy3-CEBPA.

- **Neutrophils**
  - The neutrophil populations do not uptake MTL-Cy3-CEBPA.

### Conclusion and future work

- **Conclusion**
  - MTL-Cy3-CEBPA can be taken up by some myeloid cell and CD34+ cell populations.

- **Future work**
  - To investigate the CEBPA mRNA gene expression level in the cells which uptake MTL-Cy3-CEBPA.
  - To apply our technology to target other diseases which can be treated by modulating myeloid and CD34+ cells.

### References

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