Project title:  “Investigating targeted protein degradation for leukaemia therapy”
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Research Group:  Stem Cell Biology

Acute myeloid leukaemia (AML) is a devastating blood cancer with limited treatment options and high mortality rates. We, and others, have identified a protein called MOZ/KAT6A as a potential therapeutic target, particularly in a specific subtype of AML known as MLL rearranged (MLLr) AML. An inhibitor of the catalytic activity of KAT6A (WM-1119) has entered Phase 1 clinical trials in breast, lung and prostate cancers and we, like others, have shown its effectiveness against MLLr AML in vitro. However, we have also demonstrated that it is not only the catalytic activity but also the scaffolding function of KAT6A that contributes to MLLr AML fitness. Our results suggest that degrading KAT6A may be a more efficacious therapy than simply inhibiting its catalytic activity.

The proposed PhD project aims to investigate the therapeutic potential of targeted protein degradation (TPD) of KAT6A in MLLr AML. Because KAT6A is highly expressed in breast, lung, ovarian and colorectal cancers there may be therapeutic opportunity in these solid malignancies as well. TPD is a cutting-edge research tool that includes conditional genetic degron tagging (CDT) platforms and is currently translated in clinical trials with proteolysis-targeting chimaera molecules (PROTACs). PROTACs offer advantages such as lower dosing and improved side effect profiles compared to traditional therapies.

While KAT6A PROTACs are currently being developed, CDT offers a more directly amenable genetic approach that will be implemented by introducing an inducible degradation tag to the endogenous Kat6a locus. This will allow for rapid degradation of endogenous KAT6A protein upon treatment with a specific degrader drug. This drug only affects KAT6A protein and does not affect transcription. Hence, this approach is reversible and KAT6A protein levels will recover upon discontinuation of the drug treatment. Using this CDT strategy, the student will study the temporal and quantitative requirements for KAT6A in different human MLLr-AML cell lines representing various genetic rearrangements and prognostic classifications. The goal is to define the conditions needed to induce the differentiation of these leukaemia cells (the primary therapeutic goal) through targeted protein degradation as well as to identify the subtypes of MLLr AMLs that respond the most to the treatment.

In addition to cell line studies, the PhD student will use a mouse model with a KAT6A CDT to investigate the effects of degrading KAT6A in living organisms. This will inform how KAT6A degradation impacts the growth of MLLr AML in mammals and whether it affects normal blood cell development or causes any potential side effects in other tissues. Moreover, this model will enable a deeper exploration through multi-omics analyses of KAT6A’s functions in normal blood cell development and how they are altered in cancer. Finally, the PhD student will compare, and contrast, these results to the effects of then available KAT6A PROTACs on AML. The most promising PROTAC candidates will progress to pre-clinical animal models of MLLr AML for further testing.

In summary, this project holds promise for advancing AML treatment through exploration of novel therapeutic strategies through targeted protein degradation of KAT6A as a novel therapeutic strategy. Successful development of KAT6A PROTACs could lead to more efficacious and tolerable therapies for patients, especially in vulnerable groups like children with AML. This project will provide outstanding training in the field of cellular and molecular haematopoiesis, oncology and cutting-edge technologies including targeted protein degradation, multi-omics and mouse modelling.

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