PhD Project Proposal

Funder details

Studentship funded by:	MRC DTP

Project details

Project title:	Exploring the interplay between histone acetyltransferase complexes in acute myeloid leukaemia

Supervisory team

Primary Supervisor:	Dr Alex Radzisheuskaya
Associate Supervisor(s):	Dr Tanya Trakarnphornsombat
Secondary Supervisor:	

Divisional affiliation

Primary Division:	Cancer Biology
Primary Team:	Chromatin Biology
Site:	Chelsea

Project background

Alterations in epigenetic regulators are frequently observed across various cancers. Developing therapeutic strategies targeting these aberrations requires detailed mechanistic insights into their effects on chromatin organisation and gene expression regulation. Histone acetylation is a crucial mechanism of chromatin regulation, with the acetylated state characterised by more open and accessible chromatin. Among the enzymes responsible for histone acetylation, KAT6A and KAT6B have recently emerged as potential cancer drivers, being amplified in over 10% of all cancers. A combined KAT6A/B inhibitor is currently in Phase I clinical trials for advanced and metastatic cancers, showing promising early results in a subset of breast cancer patients (Mukohara *et al.*, 2024). Additionally, KAT6A has been proposed as a therapeutic target in acute myeloid leukaemia (AML) (Su *et al.*, 2021; Yan *et al.*, 2021), an aggressive blood cancer with poor survival rates. However, only a subset of AML cell lines responds to KAT6A depletion, and the reasons for this differential response remain unknown. To address this, we conducted a synthetic lethality CRISPR screen in an AML cell line resistant to KAT6A loss, with and without KAT6A inhibitor treatment. This unpublished screen revealed that knockout of another histone acetyltransferase (HAT) complex sensitises these cells to KAT6A inhibition, suggesting a previously unrecognised redundancy between these two HAT complexes. In this project, the student will investigate the molecular mechanisms underlying this observation and explore its potential therapeutic implications.

Project aims

- Validate the identified synthetic lethal interaction across human AML cell lines with different mutational burdens.
- Evaluate the impact of the identified synthetic lethal interaction on in vivo AML development.
- Compare and contrast the genomic occupancy and target genes of synthetic lethal HATs to identify the convergent pathways.
- Profile histone acetylation patterns following the loss of synthetic lethal HATs, individually and in combination, to elucidate their overlapping catalytic activities.

Research proposal

Acute myeloid leukaemia (AML) is an aggressive disease characterised by the uncontrolled growth of immature myeloid cells in the bone marrow, blood, and occasionally other tissues. AML is the most common type of acute leukaemia in adults and accounts for 15–20% of cases in children. Although the survival rate varies greatly between different types of AML, the overall prognosis is poor, with only about 25% of patients surviving for 5 years after diagnosis. While some treatments that target specific mutations have been developed, the standard of care has not changed significantly in the past 40 years. This highlights the need for a better molecular understanding of the disease and more efficient therapy development.

The proposed project will investigate the mechanisms driving the synthetic lethal interaction between the two histone acetyltransferase (HAT) complexes in acute myeloid leukaemia, an interaction recently identified in our lab. We hypothesise that these two complexes redundantly drive histone acetylation and gene activation in AML cells and that targeting both complexes can represent a powerful therapeutic strategy.

Aim 1: Validate the synthetic lethality interaction between the two HAT complexes across AML cell lines and identify the specific subunits involved.

The two HAT complexes under investigation are multi-protein assemblies, each comprising distinct functional modules. We will identify which subunits or modules exhibit the strongest synthetic lethality when disrupted alongside the other complex. This will be achieved by employing CRISPR-mediated knockout of individual subunits in combination with chemical inhibition of the other complex. We will perform these experiments across a panel of 10 human AML cell lines with varying mutational profiles (3 sensitive and 7 resistant to inhibition of one of the complexes alone) to comprehensively validate the interaction.

Aim 2: Investigate the impact of HAT synthetic lethality on AML development in vivo.

We will utilize a mouse model of AML where subunits of one of the HAT complexes can be knocked out in a doxycycline-inducible manner. After transplantation of AML cells from these mice into recipient mice, we will induce the knockout and administer a chemical inhibitor of the other complex to assess how the dual disruption affects disease progression. Experiments will be conducted at different disease stages to determine the efficacy of this approach under varying conditions of disease burden. Additionally, we will evaluate the therapeutic potential of a PROTAC-based degradation approach targeting one of the histone acetyltransferase complexes in combination with inhibition of the other, assessing the combined efficacy in reducing AML progression.

Aim 3: Map the genomic occupancy and identify target genes of the two HAT complexes to uncover convergent pathways.

We will employ the Cut&Run technique to map the chromatin binding sites of both histone acetyltransferase complexes in AML cells. This will reveal how the loss of one complex impacts the localization of the other. RNA sequencing will also be conducted following knockout or chemical inhibition

of each complex individually and in combination. This approach will help identify the genes and pathways regulated by these complexes, shedding light on the molecular networks maintaining AML and the mechanisms driving synthetic lethality.

Aim 4: Profile histone acetylation patterns following the loss of either complex, individually and in combination, to elucidate their redundant catalytic activities.

Using the Cut&Tag technique, we will profile changes in histone acetylation marks at key genomic sites regulated by both histone acetyltransferase complexes. This will allow us to map the acetylation landscape and assess how these modifications are altered upon disruption of each complex alone or in combination. By comparing these acetylation profiles, we aim to gain deeper insights into how these complexes regulate chromatin structure and gene expression in AML, and how disrupting their activity can influence cancer progression.

Literature references

Bassi, Z.I., Fillmore, M.C., Miah, A.H., Chapman, T.D., Maller, C., Roberts, E.J., Davis, L.C., *et al.* (2018), "Modulating PCAF/GCN5 Immune Cell Function through a PROTAC Approach", *ACS Chemical Biology*, Vol. 13 No. 10, pp. 2862–2867, doi: 10.1021/acschembio.8b00705.

Gezer, D., Guitart, A.V., Vukovic, M., Subramani, C., Dunn, K., Pollard, P., Ratcliffe, P.J., *et al.* (2013), "HIF-1α Is Not Essential For The Establishment Of MLL-Leukaemic Stem Cells", *Blood*, Vol. 122 No. 21, p. 3767, doi: 10.1182/blood.v122.21.3767.3767.

Kucinski, I., Campos, J., Barile, M., Severi, F., Bohin, N., Moreira, P.N., Allen, L., *et al.* (2024), "A time- and single-cell-resolved model of murine bone marrow hematopoiesis", *Cell Stem Cell*, Vol. 31 No. 2, pp. 244-259.e10, doi: 10.1016/j.stem.2023.12.001.

Lawson, H., Holt-Martyn, J., Dembitz, V., Durko, J., Kabayama, Y., Wang, L., Lagemaat, L.V.D., *et al.* (2022), "Targeting HIF-Hydroxylases Compromises Disease Initiation and Propagation, and Synergises with Current Therapies to Eliminate Cancer Stem Cells in AML", *Blood*, Vol. 140 No. Supplement 1, pp. 8731–8732, doi: 10.1182/blood-2022-165192.

Lawson, H., Holt-Martyn, J.P., Dembitz, V., Kabayama, Y., Wang, L.M., Bellani, A., Atwal, S., *et al.* (2023), "The selective prolyl hydroxylase inhibitor IOX5 stabilizes HIF-1α and compromises development and progression of acute myeloid leukemia.", *Nature Cancer*, Vol. 5 No. 6, pp. 916–937, doi: 10.1038/s43018-024-00761-w.

Mukohara, T., Park, Y.H., Sommerhalder, D., Yonemori, K., Hamilton, E., Kim, S.-B., Kim, J.H., *et al.* (2024), "Inhibition of lysine acetyltransferase KAT6 in ER+HER2− metastatic breast cancer: a phase 1 trial", *Nature Medicine*, pp. 1–9, doi: 10.1038/s41591-024-03060-0.

Radzisheuskaya, A., Peña-Rømer, I., Lorenzini, E., Koche, R., Zhan, Y., Shliaha, P.V., Cooper, A.J., *et al.* (2023), "An alternative NURF complex sustains acute myeloid leukemia by regulating the accessibility of insulator regions.", *The EMBO Journal*, Vol. 42 No. 24, p. e114221, doi: 10.15252/embj.2023114221.

Radzisheuskaya, A., Shliaha, P.V., Grinev, V., Lorenzini, E., Kovalchuk, S., Shlyueva, D., Gorshkov, V., *et al.* (2019), "PRMT5 methylome profiling uncovers a direct link to splicing regulation in acute myeloid leukemia.", *Nature Structural & Molecular Biology*, Vol. 26 No. 11, pp. 999–1012, doi: 10.1038/s41594-019-0313-z.

Radzisheuskaya, A., Shliaha, P.V., Grinev, V.V., Shlyueva, D., Damhofer, H., Koche, R., Gorshkov, V., *et al.* (2021), "Complex-dependent histone acetyltransferase activity of KAT8 determines its role in transcription and cellular homeostasis", *MOLCEL*, Vol. 81 No. 8, pp. 1749-1765.e8, doi: 10.1016/j.molcel.2021.02.012.

Su, J., Wang, X., Bai, Y., Sun, M., Yao, Y. and Duan, Y. (2021), "The role of MOZ/KAT6A in hematological malignancies and advances in MOZ/KAT6A inhibitors", *Pharmacological Research*, Vol. 174, p. 105930, doi: 10.1016/j.phrs.2021.105930.

Yan, F., Li, J., Milosevic, J., Petroni, R., Liu, S., Shi, Z., Yuan, S., *et al.* (2021), "KAT6A and ENL form an epigenetic transcriptional control module to drive critical leukemogenic gene expression programs", *Cancer Discovery*, Vol. 12 No. 3, p. candisc.1459.2020, doi: 10.1158/2159-8290.cd-20-1459.

Candidate profile

Note: the ICR's standard minimum entry requirement is a relevant undergraduate Honours degree (First or 2:1).

Pre-requisite qualifications of applicants:

Intended learning outcomes:

- Expertise in a range of molecular and cell biology, biochemistry and genomics approaches
- Excellent understanding of chromatin regulation and cancer biology
- Project management skills
- Oral and written scientific communication skills

Advertising details

Project suitable for a student with a background in:

- ☒ Biological Sciences
- ☐ Physics or Engineering
- ☐ Chemistry
- ☐ Maths, Statistics or Epidemiology
- ☐ Computer Science