ICR The Institute of Cancer Research

PhD Project Proposal

Funder details

Studentship funded by:	Brain Tumour Research Centre of Excellence grant

Project details

Project title:	Transcription factor targeting in paediatric-type diffuse high-grade glioma

Supervisory team

Primary Supervisor:	Dr Gary Newton
Associate Supervisor(s):	Dr Lindsay Evans, Dr Lynn Bjerke
Secondary Supervisor:	Prof. Chris Jones

Divisional affiliation

Primary Division:	Cancer Therapeutics
Primary Team:	Medicinal Chemistry Team 3
Site:	Sutton

Project background

Paediatric-type diffuse high-grade glioma (PDHGG) are a collection of brain tumours in children and young adults with an extremely poor clinical outcome. For the vast majority of these tumours, the median survival is only 9-18 months, with 2-year survival rates of less than 5% of patients with certain subtypes. Much of the historical failure to improve survival in these patients stemmed from a lack of understanding of the biological differences with similar-looking tumours in adults, and within the diverse spectrum of what we call a 'high grade glioma' in the younger population. The remarkable discoveries of PDHGG harbouring driving alterations in genes previously unknown to be related to cancer, such as the oncohistone H3 mutations and somatic *ACVR1* mutations, alongside exquisite transcriptional dependencies related to the stalled developmental origins of these tumours, has highlighted the necessity for bespoke, novel strategies for therapeutic development. With the international CONNECT consortium of paediatric neuro-oncology centres, Prof Chris Jones has recently established a PDHGG Centre of Excellence, to provide the resource and focus to screen promising, hypothesis-driven concepts in well-characterised disease models with a view to generating robust preclinical data packages suitable for rapid clinical translation.

One such novel avenue is to tackle subgroup-specific dependencies identified in tumour progenitor subpopulations which may be necessary during neurodevelopment, but not later, and thus may represent unique and highly selective therapeutic targets. In diffuse hemispheric glioma with H3G34 mutations (DHG-H3G34), we have recently integrated bulk/single-cell multi-omics with genome-wide CRISPR-Cas9 screens to resolve a putative cellular hierarchy along a continuum of interneuronal development, with the majority of screening hits upregulated in progenitor-like cells along this lineage. The *DLX1/2/5/6* transcription factors, critically involved in forebrain interneuron specification, were identified as some of the most promising and well-validated hits. We are aiming to find therapeutic means of modulating these targets.

Project aims

- Identify druggable targets for treatment of high grade diffuse glioma
- Identify compounds that can interfere with the transcription of DLX family transcription factors
- Establish whether these compounds might be suitable starting points for a drug discovery programme
- Identify protein targets that can affect DLX transcription

Research proposal

The project will be a multi-disciplinary project at the interface of chemical biology, medicinal chemistry and cancer biology and will be supported by both Dr Gary Newton and Prof. Chris Jones

Stage 1

The initial aim of the project will be to identify small molecules that can interfere with DLX transcription. To do this we will build a cellular DLX reporter assay and use this to screen ICR in-house libraries to identify compounds that give the desired biological phenotype. We will screen a range of compounds from the Division of Cancer Therapeutics “Cell Permeable” library, “Drugs and Tools” library, which consist of compounds with known mechanisms, and a degrader library.

Stage 2

Once we have identified suitable starting points we will use medicinal and chemical biology approaches to:

- Make modifications to the hits to increase their potency
- Identify vectors which can tolerate linker substitution and retain activity
- Make pull down probes and PROTACs, with follow up proteomics to identify potential protein targets

Stage 3

This will involve further biological testing with the aim of validating the targets through genetic manipulation using techniques such as RNA interference and assessing whether the compounds we have identified can selectively target PDHGG.

Depending upon progress and outcomes at the different stages we may also investigate alternative approaches such as:

a) The direct targeting of DLX transcriptions factors through fragment screening and subsequent medicinal chemistry optimisation

DLX transcription factors are part of a family of proteins that contain a homeodomain (HD), a region of ~60 amino acids in length that is responsible for binding to DNA.

Crystal structure of HD Domain of DLX5 bound to DNA (PDB: 4RDU)

b) Targeting PDHGG through alternative mechanisms based on research arising from the Jones group

Literature references

[1] Jones, C., et al., *Pediatric high-grade glioma: biologically and clinically in need of new thinking.* Neuro Oncol, 2016. **19**: p. 153-161.
[2] Mackay, A., et al., *Integrated Molecular Meta-Analysis of 1,000 Pediatric High-Grade and Diffuse Intrinsic Pontine Glioma.* Cancer Cell, 2017. **32**(4): p. 520-537 e5.
[3] Mackay, A., et al., *Molecular, Pathological, Radiological, and Immune Profiling of Non-brainstem Pediatric High-Grade Glioma from the HERBY Phase II Randomized Trial.* Cancer Cell, 2018. **33**(5): p. 829-842 e5.
[4] Bjerke L, et al, *"Histone H3.3 mutations drive paediatric glioblastoma through upregulation of MYCN"* , 2013, Cancer Discov 3(5):512-519
[5] Tan, Y. and Testa, J.R. *DLX genes: Roles in development and cancer*, Cancers (Basel), 2021. **13(**12):3005. doi: 10.3390/cancers13123005
[6] Bürglin, T. et al. Homeodomain proteins: an update, Chromosoma, 2016, 125, p. 497-521

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:

BSc or MSc in discipline related to chemistry, medicinal chemistry or chemical biology

Intended learning outcomes:

- Develop skills in chemical biology and medicinal chemistry
- Develop an in-depth understanding of PDHGG biology and lineage-specific transcription factor targets.
- Develop skills as an organic chemist
- Develop the ability to test self-driven hypotheses, critically appraise relevant literature and design experiments independently using robust methodology
- Produce research outputs including project reports, conference abstracts, presentations at key meetings and peer-reviewed published papers

Advertising details

Project suitable for a student with a background in:

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