Clinical PhD Project 2024

Drugging the undruggable: Therapeutically targeting key drivers of pro- and anti-oncogenic signaling in brain cancer, lung cancer and leukemia.

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Principal supervisor's CRUK CC theme:

- Brain Cancer Virtual Institute
- Cell and Molecular Biology Programme
- Haematological Malignancies Programme
- Thoracic Cancer Programme

Department for student registration: CRUK Cambridge Institute
Department or institute where research will take place: CRUK Cambridge Institute

Postgraduate scheme: **Clinical Research Training Fellow (3-year PhD)**

PhD project outline:

Our lab integrates machine learning and high-throughput biochemistry to study how proteins selectively recognise their substrates, how this process is perturbed in cancer and how it can be hijacked to find highly selective and mutant-specific drugs to overcome drug resistance.

Our laboratory has recently made exciting progress in disentangling pro- and anti-oncogenic signalling driving cancer and in screening targets with combinatorial complete peptide libraries. In joining our laboratory's efforts to turn these binders into small molecule therapeutics, we will be attempting to not only study but also target and drug proteins that have been traditionally considered undruggable. For further information about our research group, including our computational and experimental technologies, our most recent publications, our lab values and members, and other relevant information, please visit our website: https://www.creixell-lab.com

PhD experimental plan:

In this project, we will be capitalizing on these advances to:

1. Use our peptide screen technology, so that we can screen and target resistance variants of EGFR and other kinases driving brain cancer, lung cancer and leukemia. This will consist of over-expressing and purifying these resistance-relevant mutant EGFR and other kinases. Then, we screen them against our proteome-wide and combinatorially complete libraries by peptide display to identify mutant-specific peptide and small molecule binders. Then, mathematically model the epistatic trajectories that these mutants impose when combined.
2. Identify critical vulnerabilities downstream of pro- and anti-oncogenic signalling in brain cancer, lung cancer and leukemia. Following up on our recent work in this area, we will be performing multi-targeted combinatorial CRISPR screens to test the effect of knocking down subsets of anti- or pro-oncogenic targets downstream of specific tyrosine kinases to further disentangle the causal drivers of these cancer types.

3. Further develop and expand our display technologies so that we can screen binding targets beyond protein kinases, such as Rb, Myc, Ras, Histone H3, other transcription factors, epigenetic regulators and signalling-related proteins along the MAPK pathway or more generally relevant to these processes. We will be working to consider alternative methods to enrich binders as well as “all-in-one” systems, where both the target and peptide libraries can be screened simultaneously so that all-against-all screens are possible.
4.

Main techniques:

- Protein purification and isolation
- Standard molecular biology techniques: cloning, western blot, etc.
- Bacterial peptide/kinase display, flow cytometry, immunoprecipitation, next-generation sequencing, biophysical measurements of binding, mass spectrometry
- Computational: Analysis of deep sequencing data, mathematical modelling and ideally programming

Key references:

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Rodrik-Outmezguine, V.S. et al. Nature 534, 272–276 (2016).
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Zhang, Z. et al. Cancer Cell 40, 1060–1069 (2022).
Zhao, B. et al. Cell 165, 234–246 (2016).