Do small cell lung cancers exploit developmental mechanisms?

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Principal supervisor's CRUK CC theme:

- Cell and Molecular Biology Programme
- Thoracic Cancer Programme
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Department for student registration: PDN
Department or institute where research will take place: Gurdon Institute

Postgraduate scheme:

- **MRes + PhD (1 + 3-year non-clinical applicants)**
- **Part-time MRes + PhD (2 + 3-year clinical applicants)**

MRes project outline:

Small Cell Lung Cancers (SCLC) are highly phenotypically heterogeneous and rapidly become refractory to chemotherapy with a 5 year survival rate of <7% (Byers and Rudin 2015). There are four major histological types defined by expression of key transcription factors (TFs): ASCL1+, NEUROD1+, POU2F3+ and TF-low (Gay et al. 2021). However, despite the phenotypic heterogeneity, nearly all tumours result from loss of P53 and RB. Mouse models suggest that the ASCL1+ and NEUROD1+ sub-types arise from neuroendocrine cells and are associated with distinct levels of MYC activation (Ireland et al. 2020). Whereas the rarer POU2F3+ sub-type is believed to arise in the rare chemosensory brush cells. NEUROD1 expression has never been detected in the normal adult human airways, or the developing and adult mouse lung. Our lab has just completed a single cell RNA sequencing atlas study of the developing human lungs which has revealed the existence of two neuroendocrine cell types with distinct ASCL1+, or NEUROD1+, gene expression profiles (He et al. 2022). This leads to two hypotheses. Firstly, that in the human adult lungs two distinct neuroendocrine cell populations are the cell of origin of the ASCL1+ and NEUROD1+ NSCLCs respectively. Alternatively, although not mutually exclusively, the SCLCs exploit developmental mechanisms to exhibit phenotypic plasticity (Gupta et al. 2019). Both scenarios have implications for developing targeted cancer treatment strategies.

In this rotation project we aim to test the hypothesis that activating the same pattern of oncogenes in the two neuroendocrine cell types in organoid models will result in tumoroids with distinct cancer phenotypes.

MRes experimental plan:

We have already developed unpublished methods for differentiating both types of human neuroendocrine cell sub-types from our easily-manipulable human lung organoid system (Sun et al. 2021; Nikolić et al. 2017).

We will use CRISPR-editing to sequentially introduce mutations in P53, RB and MYC into the neuroendocrine cell organoids and assess the phenotype of the resulting tumoroids. Analysis will

include organoid and cell morphology, proliferation rates, colony forming assays, and gene expression profiling via qRT-PCR.

PhD project outline:

In the longer-term this project will investigate the roles of developmental pathways and external perturbations in the observed phenotypic plasticity of SCLCs, using in vitro and xenografted human cell models and analyses of primary resected tumours.

PhD experimental plan:

SCLC phenotypic plasticity will be investigated using organoid models, incorporation of tumour microenvironment, and the response to drug treatment.

Main techniques:

Organoids, CRISPR, mouse models; histology, single cell sequencing

Key references:

Byers, Lauren Averett, and Charles M. Rudin. 2015. “Small Cell Lung Cancer: Where Do We Go from Here?” Cancer 121 (5): 664–72.
Gay, Carl M., C. Allison Stewart, Elizabeth M. Park, Lixia Diao, Sarah M. Groves, Simon Heeke, Barzin Y. Nabet, et al. 2021. “Patterns of Transcription Factor Programs and Immune Pathway Activation Define Four Major Subtypes of SCLC with Distinct Therapeutic Vulnerabilities.” Cancer Cell 39 (3): 346-360.e7.

Gupta, Piyush B., Ievgenia Pastushenko, Adam Skibinski, Cedric Blanpain, and Charlotte Kuperwasser. 2019. “Phenotypic Plasticity: Driver of Cancer Initiation, Progression, and Therapy Resistance.” Cell Stem Cell 24 (1): 65–78.

He P, Lim K, Sun D, Pett JP, Jeng Q, Polanski K, Dong Z, Bolt L, Richardson L, Mamanova L, Dabrowska M, Wilbrey-Clark A, Madissoon E, Tuong ZK, Dann E, Suo C, Kai’En IG, He X, Barker B, Teichmann SA, Marioni J, Meyer KB, Rawlins EL. (2022) A human fetal lung cell atlas uncovers proximal-distal gradients of differentiation and key regulators of epithelial fates. Cell 185: 4841-4860, doi.org/10.1016/j.cell.2022.11.005

Ireland, Abbie S., Alexi M. Micinski, David W. Kastner, Bingqian Guo, Sarah J. Wait, Kyle B. Spainhower, Christopher C. Conley, et al. 2020. “MYC Drives Temporal Evolution of Small Cell Lung Cancer Subtypes by Reprogramming Neuroendocrine Fate.” Cancer Cell 38 (1): 60-78.e12.

Nikolić, Marko Z., Oriol Caritg, Quitz Jeng, Jo-Anne Johnson, Dawei Sun, Kate J. Howell, Jane L. Brady, et al. 2017. “Human Embryonic Lung Epithelial Tips Are Multipotent Progenitors That Can Be Expanded in Vitro as Long-Term Self-Renewing Organoids.” ELife 6 (June). https://doi.org/10.7554/eLife.26575.

Sun, Dawei, Lewis Evans, Kyungtae Lim, and Emma L. Rawlins. 2021. “A Functional Genetic Toolbox for Human Tissue-Derived Organoids.” BioRxiv. https://doi.org/10.1101/2020.05.04.076067.