Resolving the isoform-specific signalling of RSK1 and RSK4 in non-small cell lung cancer through combined artificial intelligence and molecular biology

Supervisors:

Dr Olivier Pardo, Imperial College London, Department of Surgery and Cancer

Dr Kirill Veselkov, Imperial College London, Department of Surgery and Cancer

Dr Paul Huang, Institute of Cancer Research, Division of Molecular Pathology

Professor Michael Seckl, Imperial College London, Department of Surgery and Cancer

Research Summary

Non-small cell lung cancer (NSCLC) is the most prevalent lung cancer subtype. Despite the successful introduction of immunotherapy for treatment of this disease[1], most patients still subsequently require chemotherapy and die of metastatic disease. Hence, NSCLC is an area of urgent therapeutic need. RSKs (p90 ribosomal S6 kinases), of which four isoforms exist in humans (RSK1 to 4), are serine/threonine-kinases involved in multiple biological processes[2]. We showed that downregulation of RSK1 and RSK4 had opposite effects on cell invasiveness and drug response in NSCLC. RSK4 silencing prevented metastasis and sensitised to chemotherapy while that of RSK1 promoted invasiveness and drug resistance[3,4]. Overexpression of these kinases had the converse effects[3,4]. This is clinically significant as we found RSK4 overexpressed in ~60% of NSCLC and RSK1 downregulated in NSCLC metastasis[3,4]. Also, high RSK4 expression correlates with poor prognosis in lung adenocarcinoma patients while that of RSK1 correlates with improved overall survival in lung cancer[4]. So, despite high protein sequence homology (~85%), RSK1 and 4 show several divergent biological functions in lung cancer and we demonstrated that targeting RSK4 selectively, using one of our allosteric activation inhibitors, is of therapeutic benefit in vivo[4] . While the opposite effects of RSK1 and 4 associate with differential regulation of apoptotic and cell migration processes, selective signalling mediators of the two kinases explaining these discrepancies are unknown.

Through our proposed multidisciplinary project that combines molecular biology and artificial intelligence, we intend to identify these mediators as this knowledge would have direct translational relevance. Indeed, it would reveal new therapeutic opportunities that could substitute for direct RSK4 inhibition in case of *de novo*/acquired resistance to our inhibitors for this kinase or synergise with them by targeting complementary nodes in the same pathway.

Specific Aims

We will

- Identify selective substrates and interactors of RSK1 and RSK4,
- Use statistical inference and network artificial intelligence to highlight differentially-regulated pathways downstream of each kinase, and
- Validate the most promising targets/pathways in a panel of NSCLC cell lines.

We will primarily use A549 and PC9 cells, representing two common oncogenic drivers in NSCLC (KRAS and EGFR activating mutations, respectively). Validation experiments will use additional NSCLC cell lines with varied genetic make-up. We anticipate that the outcome of this work will show for the first time comprehensively profile pathways underlying common and selective functions of RSK1 and RSK4 in NSCLC. This will deliver better understanding of how these kinases impact cancer progression and provide potential biomarkers for therapeutic targeting of RSK4. It will also develop our existing AI models to include signalling directionality and propose novel drug combinations for NSCLC. Hence, this work will be a reference on how combining AI and molecular biology approaches can be used to improve cancer therapy.

The student will be embedded into multidisciplinary research teams across the two institutions with extensive experience in the various aspects of the research and able to provide the required theoretical and practical training. The Pardo/Seckl lab has extensive experience in the identification of novel protein-protein interactions and kinase-substrate pairs by proteomics approaches. The proteomics aspect of the work will be supported by Paul Huang, who has extensive experience in various mass-spectrometric-based proteomics. Kirill Veselkov is actively involved in teaching informatics techniques, programming, and network-based machine learning (NML) at Imperial College and is a world-leader in the use of NML to infer new therapeutic approaches for cancer. The supervising team has overlapping yet distinct skill sets that will enable the integrated training of the recruited student.

Literature references

1. *Denault, M. H. & Melosky, B. Immunotherapy in the First-Line Setting in Wild-Type NSCLC. Curr Oncol 28, 4457-4470 (2021). https://doi.org:10.3390/curroncol28060378*
2. *Lara, R., Seckl, M. J. & Pardo, O. E. The p90 RSK family members: common functions and isoform specificity. Cancer Res 73, 5301-5308 (2013). https://doi.org:10.1158/0008-5472.CAN-12-4448*
3. *Lara, R. et al. An siRNA screen identifies RSK1 as a key modulator of lung cancer metastasis. Oncogene (2011). https://doi.org:onc201161 [pii]10.1038/onc.2011.61*
4. *Chrysostomou, S. et al. Repurposed floxacins targeting RSK4 prevent chemoresistance and metastasis in lung and bladder cancer. Sci Transl Med 13 (2021). https://doi.org:10.1126/scitranslmed.aba4627*

Person specification

This project is suitable for a talented graduate or undergraduate student with life sciences, or computer science background. The standard minimum entry requirement is a relevant undergraduate honours degree (First or 2:1). We particularly welcome British applicants from Black and ethnic minority backgrounds, as they are underrepresented at PhD level within Imperial College and The Institute of Cancer Research.

The studentship will be registered at Imperial College London with affiliate status at the Institute of Cancer Research. The student will have access to both institutions and benefit from the world class research infrastructure and expertise across the two institutions. The student will become a member of the CRUK Convergence Science Centre PhD cohort which is a unique group of students working across distinct disciplines to tackle the big problems in cancer. A unique convergence science training programme will provide the skills and language to navigate different disciplines.

Funding and duration

Studentships will be for four years commencing in October 2023. Successful candidates will undertake a four-year research training programme under the guidance of the supervisory team. Students will receive an annual stipend, currently £23,000 per annum and project costs paid for the four-year duration. Convergence Science PhDs cover tuition fees for UK students only. Funding for overseas fees is not provided, international students are invited to apply subject to outlining how they will meet the difference in tuition fees.