Unlocking the KLK activome in drug-resistant cancer: imaging, biomarkers and target validation using novel activity probes

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Summary

This 4-year PhD studentship is funded by Cancer Research UK, and is open to all residents of the European Union; it offers an enhanced tax-free stipend of £21000 pa, plus support for conference travel. The project would ideally suit an outstanding Masters level chemist, medicinal chemist or chemical biologist, with some research experience in synthetic chemistry and/or chemical biology, and a strong interest in developing and applying novel chemical tools in the context of cancer diagnostics and therapeutics.

Kallikrein-related peptidases (KLKs) are a family of 15 secreted serine proteases which form a network – the KLK activome – with a versatile and crucial role in extracellular proteolysis and signalling. Whilst KLK3 (prostate specific antigen, PSA) is used as a prognostic, diagnostic and monitoring biomarker for prostate cancer, many other KLKs are also deregulated in prostate (KLK2, 4, 5, 7, 11 and 12) and ovarian (KLK4, 6 and 10), as well as in gastric and breast cancers.

The KLK activome offers an exciting opportunity for biomarker discovery, imaging and therapeutic intervention. However, the catalytic activity of the KLKs is controlled by intricate post-transcriptional and post-translational regulation, preventing an effective understanding of the dynamics of physiological KLK activity in cells or in vivo. A new approach to understand KLK network activity in a living system is needed to unlock the full potential of KLKs as targets in cancer, and we have recently developed a new class of chemical activity-based probes (ABPs) with the unique capacity to detect and quantify the activity of specific KLKs in a physiological setting. The chemical tools offer for the first time the potential to directly profile the KLK activome in a living cell, in complex 3D cancer models, or in a whole organism.

As the student on this project you will be at the centre of a multidisciplinary collaboration to develop a versatile chemical probe platform for the KLK activome in prostate and ovarian cancers. You will design, synthesise and test optimised probes for specific KLKs through a combination of solution and solid phase chemistries, and advanced high-throughput screens. You will apply these chemical proteomic tools to understand KLK dynamics, identify KLK activity biomarkers, image KLK activities in cells and in preclinical animal models, and drive validation of potential drug targets.

You will receive training in all relevant aspects of chemical synthesis, protein biochemistry, cell biology, proteomics, cancer biology, imaging and in vivo models. You will also benefit from membership of the Imperial College CRUK Centre, and the Ovarian Cancer Action Research Centre at Hammersmith Hospital involved in coordinating international clinical trials consortia of upwards of 40 trial centres, and the NIHR Imperial Biomedical Research Centre.