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editorial

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Sharpening the focus on cancer tumours

Cancer is one of the most pressing public health concerns; it is widely reported that the disease is responsible for one in every four deaths in the UK. It has been estimated that earlier diagnosis of cancer could save the NHS more than £200M per year, combining this with accurate prediction of therapeutic sensitivity or resistance of tumours would lead to significant further savings.

Cancer Research UK's Grand Challenge is the most ambitious cancer research grant in the world. It is a series of £20 million awards for international, multidisciplinary teams willing to take on the toughest challenges in cancer, providing the freedom to try novel approaches, at scale, in the pursuit of life changing discoveries. The Rosetta project, of which I am the lead, is one of Cancer Research UK's Grand Challenges, and aims to develop new, more effective treatment strategies for cancer by using innovative mass spectrometry approaches to map the chemical composition of tumours in unprecedented detail. The changes in metabolism of the tumour can have a massive impact on its overall state and function, are the key to understanding and unlocking the most effective treatments.

Mass spectrometry is a powerful investigative tool which can identify the chemicals present in tissues and tumours, based on the mass of molecules. The National Physical Laboratory (NPL) is home to the National Centre of Excellence in Mass Spectrometry Imaging (NiCE-MSI), and is an impressive source of expertise and state of the art equipment in Secondary Ion Mass Spectrometry (SIMS) and Matrix Assisted Laser Desorption/Ionisation Mass Spectrometry (MALDI-MS), as well as other techniques, including Desorption Electrospray Ionisation (DESI) and Rapid Evaporative Ionisation Mass Spectrometry (REIMS), both of which were invented by Rosetta consortium partner Professor Zoltan Takats.

The fact that we have an incomplete picture of the molecular make-up of tumours is a significant barrier in our search for treatment. We do know that tiny changes in the metabolism of a tumour can have a massive impact on its overall state and function. These changes may be due to genetic mutations and may alter the composition and distribution of metabolites. The Rosetta project aims to observe and understand these changes in metabolism using a range of accurate MS techniques. There is huge potential to use mass spectrometry data to gain new insights into how tumours develop, and for monitoring and understanding the response and/or resistance to treatment.

Mass spectrometry is the ideal investigation tool. It separates the constituent parts of a sample according to their mass-to-charge ratio, and can be used to provide both qualitative and quantitative information. Using a suite of the most advanced MSI techniques, the Rosetta project team scan relatively large areas of tissues and tumours, before focusing in greater detail using much slower, more expensive and time-consuming imaging methods to establish the chemical composition at a cellular and sub-cellular level.

MALDI and DESI platforms both enable the spatially-resolved detection of metabolites from surfaces of thin tissue sections. Molecules are either ionised via a focused electrospray of a volatile solvent (DESI), or via the assistance of a 'matrix' compound applied to the tissue (MALDI), which is irradiated with a laser. Both these methods can be used to image unlabelled molecules, so hundreds or thousands of molecules can be surveyed in a single experiment. They also have the advantage being relatively high-throughput methods that enable the rapid analysis of tissue samples to identify particular areas of interest, for instance, an area of drug resistance.

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The team then deploy Nanoscale Secondary Ion Mass Spectrometry (Nano SIMS), which offers the highest lateral resolution possible, to image labelled metabolites at an intracellular level. In addition, the consortium is using imaging mass cytometry (the study of cell characteristics and properties) for high-resolution imaging of proteins in the same samples, via metal tagged antibodies. Bringing these techniques together allows the team to generate maps of both small and large molecules on a range of scales, which when viewed together provide a 'Google Earth view' of tumour metabolism.

The Rosetta consortium is currently establishing routines for superimposing these data, which will all be made freely available to the research community. Maps that reveal information about the underlying genetic profile of the cells are expected to improve understanding of the mechanisms associated with mutational drivers of disease.

The project is already yielding remarkable results. In the first phase of the project the 'pipeline' approach was validated, meaning that the different techniques were compared, and the imaging sensitivity assessed across different instruments. The combination of MSI techniques has already provided a valuable insight into the distribution of metabolites within tumours, highlighting hot-spots of drug resistance and yielding new information about the tumours. The first year of the project has already revealed a promising avenue for better understanding drug resistance, and this has been validated through work with AstraZeneca.

Great progress is being made into investigating the mutational drivers for cancer and the activation of key pathways. As the project nears the end of its second year, the consortium is ready to take this to the next phase, which will look at a range of drug therapies, start to explore metastatic cancers, and review the data. From the results so far, it is anticipated that the project will improve the understanding of how pre-clinical model data translate to human disease.

The consortium is definitely on the road towards using the imaging pipeline to identify novel targets for drug development and providing accurate methods for diagnosis and monitoring treatment. The consortium and partners are excited to see how these approaches can be used for predicting therapeutic responses in these cancers.

The research relies on state-of-the-art measurements and instrumentation based at NPL, in collaboration with Imperial College London, AstraZeneca, Barts Cancer Institute and the University of Cambridge. The consortium is studying cancer models from cancer biology experts at the Francis Crick Institute, the Institute for Cancer Research, and the CRUK Beatson Institute. Importantly, all the data will be freely available to the research community, removing the barriers to supercharging the discovery of drugs to treat cancers. The Rosetta project is also working with other CRUK Grand Challenge teams to analyse their samples and share information.