

SCIENCE IS CHALLENGING CANCER USING THE UK'S SYNCHROTRON



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The limitations of chemotherapy and radiotherapy are driving a global search for novel ways to prevent and treat cancers. And this is why many international research teams are coming to Oxfordshire to use Diamond Light Source, the UK's national synchrotron to investigate many new approaches. Their common goal is to reduce the global impact of cancer by improving our understanding of cancer mechanisms and producing new opportunities for effective cancer therapies.

Diamond is providing industrial and academic user communities with access to state-of-the-art analytical tools to enable world-changing science. Shaped like a huge ring, it works like a giant microscope, accelerating electrons to near light speed, to produce a light 10 billion times brighter than the Sun, which is then directed off into 33 laboratories known as 'beamlines'.

In the last two years alone, Diamond has published over 345 publications related to cancer research. A particular focus has been on utilising the immune system to become more efficient in targeting cancer cells and designing new targeted therapies, the hunt for a universal cancer vaccine, tackling triple negative breast cancer, developing new hope for pancreatic cancer and non-invasive diagnosis of prostate cancer to name just some of the breakthroughs being made. Recent examples conducted by international teams in collaboration with Diamond and its scientists include:-

CANCER CELLS HAVE WAYS TO EVADE THE HUMAN IMMUNE SYSTEM

The human immune system has cells that can attack invading pathogens, protecting us from bacteria and viruses. These cells are also capable of killing cancer cells, but they don't. Cancer cells have evolved defence mechanisms to prevent them being destroyed by our immune system, allowing them to survive and replicate, growing into tumours that spread through the body. Researchers around the world are looking at different ways to overcome these complex mechanisms.

Some exciting new work analyses how breast cancer cells evade the human immune system and could leave them with nowhere to hide. Dr Rohanah Hussain and Prof Giuliano Siligardi of Diamond's B23 beamline in collaboration with an international research team led by Dr Vadim Sumbayev investigated these complex defence mechanisms of the human immune system and how cancer cells in breast tumours avoid it. They used Synchrotron Radiation Circular

Dichroism (SRCD) spectroscopy on beamline B23 to investigate these defence mechanisms.

"Our findings demonstrate the activity of the Tim-3-galectin-9 biochemical pathway in several types of human cancer cells and its possible role in the suppression of the immune system response. We found breast tumours express significantly higher levels of Tim-3 and galectin-9 than healthy tissue revealing increased levels of these key proteins in nine other cancers, highlighting their important role in cancer development. Our ultimate goal is now to find the best way to disable the Tim-3-galectin-9.

This could lead to therapies that allow our immune systems to reboot, reducing the need for more toxic treatments such as chemotherapy and radiotherapy, which have severe side-effects for patients." Explains Dr Sumbayev adding that.

The team are already planning another visit to Diamond, for the next stage in this vital research to discover the best way to disable the pathway to allow the immune system to attack cancer

cells. "Access to Diamond is crucial to our research. The sensitivity that synchrotron radiation allows cannot be replicated using other techniques, and it allows us to really see what's happening to the proteins, even small details."

USING MONOCLONAL ANTIBODIES TO MODULATE IMMUNE RESPONSE

Another promising new approach to cancer therapy is the use of monoclonal antibodies (mAbs) to modulate the immune response and improve the body's ability to destroy cancer cells. To date however use of mAbs such as urelumab has been limited due to intolerable side-effects. An international team redesigned a 4-1BB molecule to form an antibody that had potent stimulatory activity with no associated toxicity. They used High Throughput Small Angle X-ray Scattering (SAXS) on beamline B21 as part of their research. **This novel approach may unlock the potential of immunotherapeutic antibodies in cancer treatment with minimal side-effects.**

THE HUNT FOR A UNIVERSAL CANCER VACCINE

Therapeutic vaccination against tumour-associated antigens (TAA) has been a highly anticipated approach where a patient's own immune system is boosted to treat cancer, in particular harnessing the anti-cancer potential of CD8 cytotoxic T-lymphocytes but to date results have been largely disappointing. However, a team from the Universities of Cardiff and Copenhagen identified and refined 'super-agonist altered peptide ligands' (APLs) from the blood of healthy donors and were also able to induce T-cells from the blood of patients with

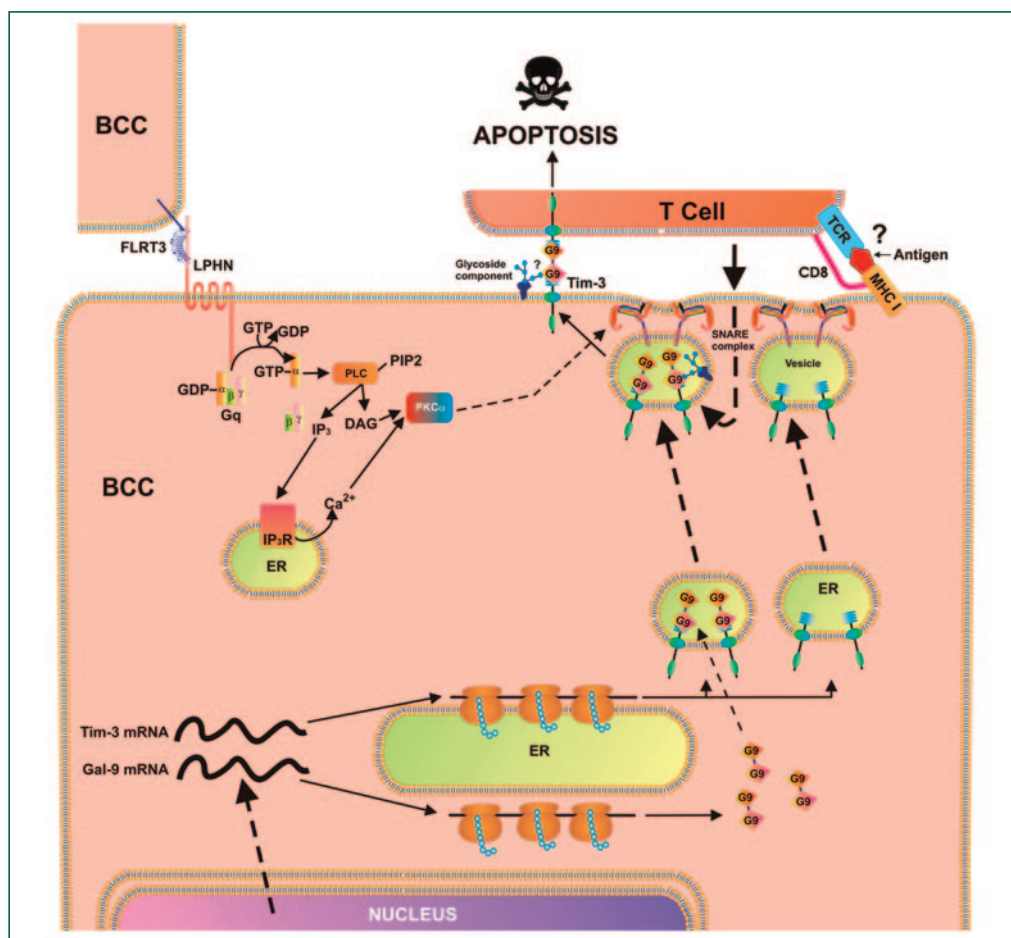
melanoma. Among other methods, the team used macromolecular crystallography on beamline I24 to generate the peptide structures. These APLs were capable of inducing T-cells with greater effectiveness and suggest that this could be a promising approach in the hunt for a universal cancer vaccine.

TACKLING TRIPLE NEGATIVE BREAST CANCER

A diagnosis of triple negative (TN) breast cancer means that the tumour does not have the three most common types of receptor that promotes tumour growth. Common therapies for this cancer type are therefore ineffective and patients have a poor prognosis.

extremely efficient vectors for intracellular delivery but have been associated with undesirable side-effects including mortality in some cases. Recently, much safer synthetic analogues for viruses have been developed. A University of Sheffield research group has designed synthetic Dengue virus-mimicking nanoparticles to selectively target TN breast cancer cells and show that genetic material can be efficiently delivered to the cell nuclei while maintaining high cell viability. They used small angle X-ray scattering and diffraction (SAXS) analysis on beamline I22 to accurately characterise the nanoparticles. **This work shows potential for new therapeutic approaches for the treatment of TN breast cancer.**

Pancreatic ductal adenocarcinoma (PDA) is difficult-to-treat cancer characterised by immune tolerance and resistance to immunotherapies including T-cell checkpoint-based immunotherapy which is becoming the standard of care for several cancers. A team of US researchers discovered upregulation of the protein kinase RIP1 in tumour-associated macrophages in PDA, a promising target in PDA. They developed a selective small-molecule RIP1 inhibitor and used macromolecular crystallography on beamline I02 to show that RIP1 inhibition is protective against pancreatic cancer in vivo. The teams research suggests that **RIP1 could be regarded as an**



Efforts are being made to design new therapies and researchers are looking at the capability of viruses to deliver effective therapies. Viruses are

NEW HOPE IN TREATING PANCREATIC CANCER

Pancreatic cancer is a particularly difficult cancer to treat with no effective therapies.

immune checkpoint and supports RIP1 inhibition as a potential new therapeutic avenue in the treatment of PDA.

Another international study investigated several new compounds for their anti-pancreatic cancer activity. The team focused their attention on dysregulation of discoidin domain receptors (DDR2) involved in several cellular processes including cell differentiation and adhesion often detected in cancer. The crystallographic structure of DDR1 was determined on beamline I04. The team designed and used a DDR1 inhibitor to successfully slow pancreatic cancer progression and to improve sensitivity to standard of care pancreatic cancer therapies. **DDR1 is now being considered as a novel target for drug discovery against pancreatic cancer.**

DEVELOPING NON-INVASIVE DIAGNOSIS OF PROSTATE CANCER

Zinc concentration is a known biomarker for prostate cancer, markedly reduced in cancer while remaining high in benign conditions. Until recently zinc concentration could only be measured using a tissue biopsy, but a research team from the University of Texas has been exploring non-invasive imaging methods using magnetic resonance imaging (MRI) and synchrotron radiation X-ray fluorescence (μ SR-XRF). Using a zinc responsive contrast agent to

detect zinc release in the prostate in a mouse model, they confirmed that zinc concentration was associated with the presence of malignant tissue. The team worked on beamline I18 during the study and highlighted the advantage of using MRI to characterise the distribution and trafficking of zinc in healthy and malignant prostate tissue. **These initial studies may provide an important way forward for the early diagnosis and treatment of prostate disease.**

A NEW APPROACH TO NON-SMALL CELL LUNG CANCER

The RAS/MAPK pathway is a major driver of oncogenesis leading to the growth of tumours and is imperfectly or abnormally regulated in approximately 30% of human cancers, primarily by mutations in the BRAF or RAS genes. The extracellular-signal-regulated kinases (ERK1 and ERK2) serve as central nodes within this pathway. An industry research group used a structure-based design approach and macromolecular crystallography on beamline I04 to identify appropriate ERK1/ERK2 inhibitors. The research led to the identification of AZD0364, a potent and selective ERK1/2 inhibitor which prevents activation of ERK1/2. The compound exhibits high cellular

potency and good pharmacological properties and has demonstrated encouraging anti-tumour activity in pre-clinical models of non-small cell lung cancer. Clinical trials on this new compound are planned to commence soon.

CEO of Diamond, Professor Andrew Harrison concludes; "Diamond serves as an agent of change, addressing 21st century challenges such as disease, clean energy, food security and more. In particular, research taking place at Diamond is improving our understanding of cancer mechanisms and producing new opportunities for effective cancer therapies.

Since operations started in 2007, more than 14,000 researchers from both academia and industry have used our world-leading facilities to conduct experiments and over 8,000 scientific articles have been published by our users and scientists."

UNDERSTANDING THE EPSTEIN BARR VIRUS PORTAL

The Epstein-Barr virus, which belongs to the herpesvirus family, is one of the most widespread human viruses and the main cause of glandular fever (infectious mononucleosis). In addition, it causes several kinds of cancer,

including Burkitt and Hodgkin's lymphoma, stomach cancer and nasopharyngeal cancer, as well as several autoimmune diseases. There is currently no treatment for infections caused by this virus.

An international team of researchers studied the structure of a key protein in the virus known as a portal which is the entrance and exit point for the viral genome. The team solved the structure of the portal at 3.5 Angstrom resolution using the Titan Krios I electron microscope in eBIC. This is the Electron Bio-Imaging Centre at Diamond which provides scientists with state-of-the-art experimental equipment and expertise in the field of cryo-electron microscopy, for single particle analysis and cryo-tomography. Two powerful cryoelectron microscopes allow users to investigate the structure of individual cells and to visualise single bio-molecules, exploiting techniques that are rarely available at home laboratories.

The detailed architecture of this protein that the team achieved suggests that it plays a functional role in DNA retention during packaging. New understanding of the portal structure paves the way for the rational design of inhibitors for the treatment of cancers.



ABOUT DIAMOND LIGHT SOURCE: WWW.DIAMOND.AC.UK

Funded by the UK Government through the Science and Technology Facilities Council (STFC), and by the Wellcome Trust, Diamond is one of the most advanced scientific facilities in the world, and its pioneering capabilities are helping to keep the UK at the forefront of scientific research.