Novel kinase inhibitors offer fresh treatment hope for prostate and pancreatic cancer

Mutations to kinase genes are associated with a range of diseases, including many cancers. Increased IKKα kinase levels have been identified as a key factor in both advanced prostate and pancreatic cancer progression, for which there are a lack of effective treatments available and an often devastating prognosis for patients. **Professor Simon Mackay** from the University of Strathclyde has developed two novel, first-in-class IKKα kinase inhibitors, which specifically target the aberrant cancer-promoting signalling protein. These new compounds have the potential to not only treat several other cancers, but also a range of inflammatory diseases, including arthritis.

Prostate cancer accounts for 36,000 new cases each year and around 10,000 deaths annually. This high mortality rate is not helped by the limited efficacy of current treatments. In fact, 80% of patients with an advanced form of the disease, who are treated with the standard androgen ablation therapy, go on to develop castrate-resistant prostate cancer (CRPC) – an incurable form of prostate cancer. Although newer, second-line therapies such as enzalutamide and abiraterone, and chemotherapies such as taxanes have extended CRPC patient survival, mortality rates are still high.

TARGETING SMALL MOLECULES TO SPECIFIC PATHWAYS

Encoded within the human genome are about 500 kinase proteins, which act as enzymes critical to cell function. It is when these proteins go awry that diseases, including many cancers, can occur. Prof Mackay is working towards developing a series of inhibitors aimed at a member of the kinase family known as IKKα. Intracellular signalling and activation of the pathway that IKKα is involved in has been identified as a key factor in the progression of prostate cancer from a hormone-dependent to castrate-resistant pathology. Until now, no attempts have been made to directly intervene therapeutically in the IKKα-associated mechanisms of cancer development. This provides a promising opportunity for the design of novel compounds, as the targeted inhibition of IKKα could turn off key signalling pathways that promote cancer cell survival, growth and proliferation.

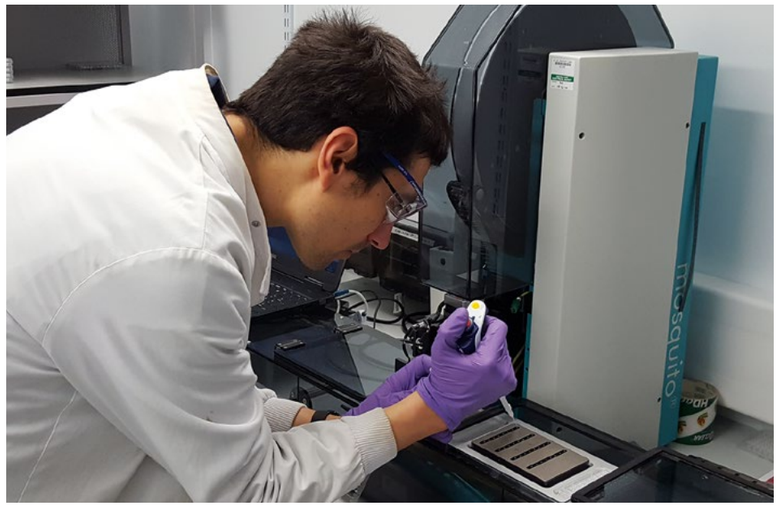
Currently, treating prostate cancer usually involves androgen ablation therapies – a treatment approach that often leads to resistance and relapse. This failure has been related to IKKα activity – IKKα regulates the inflammatory processes that occur when primary prostate cancer cells die, which is associated with the failure of androgen ablation therapy and the progression of the cancer to the castrate-resistant form. Other new drug treatments that have been approved in recent years have been primarily focused on decreasing circulating androgen levels and androgen receptor inhibition, and although these have been relatively successful, they on average still only extend survival by approximately eighteen months. By targeting the underlying processes associated with the development of CRPC, Prof Mackay's novel class of IKKα inhibitors offer a new therapeutic intervention strategy for patients if it can be successfully introduced into the clinic.

JOINT PANCREATIC CANCER FOCUS

In addition to prostate cancer, their efforts to develop this novel class of drugs are

Intervening in IKKα-associated mechanisms provides a promising opportunity for the design of novel compounds, as the targeted inhibition could turn off some of the signals that promote cancer cell survival

also aimed at tackling pancreatic cancer. As with CRPC, the IKKα regulated pathway has been found to be similarly amplified in pancreatic cancer, therefore providing an ideal target for intervention with an inhibitor. At present, the mortality rate within five years of diagnosis of advanced pancreatic cancer is shockingly high at 94–96%. There are an estimated 9,000 new cases every year in the UK and, due to inadequate screening and a lack of early clinical symptoms, most patients present with an advanced stage of the cancer, rendering it untreatable due to a lack of existing options.



DISCOVERING NEW FIRST-IN-CLASS SELECTIVE INHIBITORS

After identifying promising compounds, Prof Mackay and his team set to work on improving the properties of these molecules, enhancing their inhibitory activity and suitability for use as drugs, without compromising on potency or specificity. Unspecific kinase activity is a high risk due to the critical roles kinases play in healthy cellular pathways. In fact, off-target kinase inhibition can result in highly toxic effects, which is the reason why many similar drugs never make it through clinical trials. Despite these challenges, Prof Mackay and his research team have succeeded in producing two lead compounds, and are close to satisfying the criteria for further drug development.

The first of the optimised compounds exhibits greatly improved potency for inhibiting IKKα. This comes after the researchers demonstrated that the compound could reduce and inhibit proliferation of cell lines derived from advanced prostate cancers. However, its water solubility needs to be improved as the researchers hope to develop a drug that can be taken orally. Therefore, they are continuing development to see if they can optimise the structure and formulation to produce a more water-soluble form.

The second lead compound exhibits increased potency and water solubility, and is also incredibly specific: it only significantly inhibited one other kinase from the hundred they tested. Tests for growth inhibition on cancer cells were also successful. The only property that requires further development prior to the next stage of trials is to reduce the compound's clearance from the body. The current compound has a higher rate of clearance than is preferred, meaning that it may be metabolised by the liver and expelled from the body. Ideally, Prof Mackay would like the drug to be able to be taken orally by patients only once a day, and therefore an optimised version of the compound that would last longer would be preferable.

BROADENING REACH OF POTENTIAL EFFICACY

As IKKα has been implicated in resistance to existing therapies, Prof Mackay and his team also carried out *in vitro* tests using the novel compounds in combination with other existing treatments to see if they would work in synergy with existing drugs. Excitingly, they found that the inhibitors have a "supra-additive" effect, with the cancer cells becoming more sensitised to the current standard treatments for both CRPC and pancreatic cancer.

Prof Mackay and his team, working in collaboration with other research groups, have also begun investigating the effectiveness of their novel compounds on other conditions known to be associated with abnormalities in IKKα function. So far, the compounds have been found to inhibit the growth of patient-derived multiple myeloma and chronic lymphocytic leukaemia *in vitro*. Not only that, but, as IKKα has been shown to be important in the development of colorectal cancer and some breast cancers, these drugs may prove to have a wider range of use in other cancers. As well as this, Prof Mackay and his team are also investigating whether the compounds could treat chronic inflammatory diseases such as rheumatoid and osteoarthritis. Although still in its early days of testing, effects look promising against key IKKα-driven processes and inflammatory markers in cells derived from patient osteoarthritic synovial tissue.

Prof Mackay's research on prostate cancer treatment has now progressed beyond the confines of cell-based studies to *in vivo* studies. Their preliminary experiments using mice with metastatic prostate cancer xenografts have yielded encouraging results, with significant tumour regression occurring.

Prof Mackay has succeeded in producing two superior kinase inhibitor compounds, and his research on prostate cancer treatment has now progressed beyond the confines of petri dishes to *in vivo* studies

Q&A

What first interested you in medicinal chemistry and what inspired you to pursue a career in research?
As an undergraduate studying Pharmacy at the University of Bath, I thoroughly enjoyed the medicinal chemistry element of the programme, and had a great set of enthusiastic lecturers who clearly loved the subject. I decided to pursue a PhD in medicinal chemistry and was lucky enough to work for Roger Waigh at the University of Manchester. Roger was a member of the academic team (with John Stenlake and George Dewar – coincidentally, all based at Strathclyde at the time) that discovered atracurium, one of a very small number of drugs developed in UK academia to make it through to clinic. Roger was an inspirational (if somewhat demanding!) supervisor, who convinced me I had what it took to pursue a career in academic drug discovery research.

What would you say are the most challenging aspects of getting from identifying a potential target to developing a compound that is viable for testing as a new drug?
I'd say that the most challenging aspect has been coming to terms with the incredible complexity of biology. Cancer is continually evolving to counter everything we throw at it and so, in the spirit of maintaining an optimistic outlook, we need to believe that even if our next experiment doesn't take us a step forward in developing a new treatment, it will at least give us a better understanding of what is evolving. So there's progress even when things seem to fail!

It is also crucial to have drug-discovery-dedicated biologists and clinicians in your team in order to succeed. Convincing funding bodies that you have a viable target and the expertise to develop compounds is also a challenge. Most of my time is spent trying to raise the necessary funding.

What steps are needed to get the new compounds through to testing in human clinical trials?
We need to demonstrate that our compounds cause tumour regression in animal models that is through engagement with the target IKKα. In parallel, we need to show there is no target-related or compound-related toxicity at concentrations that are therapeutically relevant in appropriate animal models. We also need to show that the frequency of oral dosing is reasonable, which is related to clearance. If a patient has to take a tablet too often in a day, there will be issues of compliance which will impact clinical efficacy. Ideally, we're looking for a once- or twice-daily dose regimen.

If you cannot increase the water solubility of the first lead compound and reduce the clearance of the second, is it possible to employ different methods of drug delivery and dosing schedules to use them in their current structure?
All small molecule kinase inhibitors that are currently used clinically have faced these problems during development, so I'm confident we will ultimately address them – it is just a matter of time and resources.

What are your hopes for the progress of this research over the following five years?
Ideally, by partnering with a pharmaceutical company, to get an optimised drug candidate into clinical trials in patients with cancers likely to respond to IKKα inhibition

Even if our next experiment doesn't take us a step forward in developing a new treatment, it will give us a better understanding of what is evolving

Detail

RESEARCH OBJECTIVES

Professor Mackay's research looks to develop a unique series of IKKα inhibitors into compounds that offer the therapeutic potential for use in castrate-resistant prostate cancer and potentially pancreatic cancer as well. For the past 25 years, he has been applying medicinal chemistry to drug discovery, with his primary focus being drug development in cancer.

FUNDING

Currently funded by Medical Research Council (MRC)
Originally funded by Cancer Research UK
Prostate Cancer UK

KEY TEAM MEMBERS

Dr Andrew Paul; Prof Robin Plevin; Prof Gavin Halbert; Dr Marie Boyd; Dr Joanne Edwards; Prof Colin Suckling

COLLABORATORS

Professor Neil Perkins and Dr Elaine Willmore, University of Newcastle; Professor Chris Pepper, University of Cardiff; Dr Danny Huang, Beatson Institute for Cancer Research; Dr Martin Swarbrick, Cancer Research Technology Ltd; Dr Tim Hammonds, Cancer Research Technology Ltd; Dr Aymen Idriss, University of Sheffield; Professor Michael Karin, UCSD; Dr Peter Storz, Mayo Clinic

BIO

Prof Simon Mackay is Professor of Medicinal Chemistry in the Strathclyde Institute of Pharmacy and Biomedical Sciences, at the University of Strathclyde, Scotland. He is currently the Principal Investigator of a project to develop small molecules to treat prostate cancer, with the potential to treat numerous others.

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