Can you elaborate on the overarching aims of your collaboration?

The three of us have been working on this project together for the past six years, first at the Parkville Branch of the Ludwig Institute for Cancer Research in Melbourne and then for the last two years at the Walter and Eliza Hall Institute of Medical Research (WEHI).

The Ernst lab has had a longstanding interest in understanding the molecular mechanisms that drive cancers of the digestive tract – particularly of the stomach and the colon – with the ultimate goal of discovering new ways to stop the growth of malignant cells. Inflammation, especially that which is chronic in nature, has long been recognised as a key driver of cancer development. There are a number of proteins involved in inflammation and it has been speculated that some of those playing a role may also be helping cancer cells to survive and expand.

What expertise do you each contribute to facilitate the success of this research?

We are all trained molecular biologists with a keen interest in cancer biology. Throughout our careers, we have developed many preclinical animal models that we use to study human diseases such as cancer. However, the translation of results obtained from such models into treatments is a time-consuming and expensive endeavour and requires the expertise and support of various experts with complementary skills. Therefore, our study represents a true multidisciplinary undertaking between molecular and cell biologists, cancer biologists, geneticists and bioinformaticians. Together, we have now identified a family of proteins, known as JAK kinases, and found that therapeutic interference with their activity greatly inhibits cancer growth.

Are multidisciplinary and international partnerships important for the success of your work?

In this day and age, multidisciplinary research teams are not only important, they are essential. Collaborations are at the heart of all our work and assembling the best researchers with the most relevant expertise is the cornerstone of a successful project. Establishments such as WEHI have a proud track record of enabling and facilitating these interactions, which have resulted in many examples of laboratory findings being developed into clinical compounds and successful drugs.

To what extent are the mechanisms through which JAK inhibitors treat blood disorders similar to those by which your team has shown it can treat stomach and bowel cancer?

The development of JAK inhibitors was originally triggered by the discovery of mutations in the JAK2 kinase in a group of blood disorders that is commonly referred to as myeloproliferative neoplasms and results in the uncontrolled expansion of a subtype of blood cells. Importantly it was shown that these mutations locked JAK2 in a permanently activated conformation, which led to the expansion of these blood cells. In contrast to malignant blood cells, in stomach and colon cancer JAK kinases are not mutated but remain excessively activated by a constant oversupply of cytokines, including interleukin-11, which are produced by tumours and tumour-supporting cells. Thus, despite the different mechanisms that maintain JAK kinases excessively activated in blood and gastrointestinal cancers, the net effect is the same – these kinases promote the growth of cancer cells.

How does your work studying the therapeutic potential of JAK inhibitors complement your research group’s broader aim of investigating the links between inflammation and cancer?

We still have not completely understood the myriad of intricate interactions between cancerous cells and the non-cancerous cells in the surrounding tissue or interspersed within the tumour, and how inflammation shapes the conversation between these various cell types. Our studies now suggest that therapeutic inhibition of JAK kinases, as critical mediators and enablers of inflammation, can provide an alternative and/or complementary strategy to directly target the mutated cancer cells. We hold the firm belief that many more such promising targets exist and that they will become prime candidates for translational research.
Aiming for the bullseye

At the Walter and Eliza Hall Institute of Medical Research, Australia, basic research into gastrointestinal cancers is putting forward a strong case for the future use of JAK inhibitors in targeted therapies.

ACCORDING TO A report from the World Health Organization (WHO) into worldwide cancer mortality rates, stomach and colorectal cancers are among the leading causes of death – taking over 1.4 million lives in 2012 alone. In Australia, 38 people in every 100,000 were diagnosed with these cancers in 2008, with 12 in every 100,000 proving fatal. Recently, efforts in the search for new and improved therapies for treating cancers associated with the human digestive tract have focused their attention on a family of proteins called JAK kinases. Not traditionally associated with stomach and bowel cancer treatment, the inhibition of these proteins is usually used as a strategy for treating blood disorders such as myeloproliferative neoplasms. In 2011 and 2012 respectively, the US Food and Drug Administration (FDA) approved the second generation of the small-molecule JAK inhibitors Ruxolitinib® and Tofacitinib® for treating myelofibrosis and rheumatoid arthritis, a systemic inflammatory disorder.

Despite a longstanding awareness that the immune system’s inflammation response may be strongly linked to cancer, it has only been recognised as a hallmark of the disease in recent years. With a proven track record of safe and successful JAK inhibition in patients, trials have also begun to investigate their potential in leukaemia, lymphoma and lupus therapies, but none have yet been approved for treating solid tumours. Now, investigations into the complex signalling that occurs in inflamed tissues, and its contribution to cancer development, are initiating new efforts in the search for more targeted therapeutic approaches for the treatment of bowel and stomach tumours.

At the Walter and Eliza Hall Institute of Medical Research (WEHI), Australia’s oldest institute for medical research, Drs Michael Buchert, Toby Phesse and their team leader, Associate Professor Matthias Ernst, are combining their expertise to uncover the molecular mechanisms that drive the initiation and progression of gastrointestinal cancers. By making use of advanced preclinical mouse models, the team is aiming to identify the JAK proteins that are most strongly linked to tumour growth in the digestive tract. With the identification of more relevant drug targets, therapeutics will benefit from the ability to select more tailored inhibitors and improve overall treatment tolerability.

SIGNALLING THE DISEASE

The vast majority of colon cancers can be characterised by disruption to the WNT signalling pathway. Although this is an essential player in a range of physiological processes, one of its key functions is to maintain intestinal homeostasis. By promoting the continuous renewal of the epithelial cell lining of the gut, it acts as a crucial obstacle to the onset of inflammatory bowel disease and colon cancer. An important component of the WNT pathway is the tumour suppressor gene adenomatous polyposis coli (APC), and it is in this gene that mutations can aberrantly activate WNT signalling and trigger tumourigenesis. Although it provides a seemingly large bullseye for therapeutic administration, the current precision of treatments is not sufficient for targeting cancer cells specifically. “There is an inherent risk of severe side effects if one was to therapeutically target the WNT pathway directly,” explains Buchert. It is this knowledge that has set the team looking for pathways that are redundant in normal intestinal cells but critical for the proliferation and survival of WNT-dependent tumour cells.

The researchers have identified the gp130/JAK/STAT3 signalling pathway that also plays a beneficial role in wound healing and regeneration of the lining of the gut and, crucially, can be hijacked by cancer cells to promote their own growth. Since gp130/JAK/STAT3 signalling is largely dispensable for the maintenance of a healthy gut, it represents an alternative therapeutic target that could lead to less severe side effects than targeting WNT signalling directly. Recently, the team’s attention has focused on the STAT3 transcription factor associated with the pathway. Investigations have revealed it promotes the survival and proliferation of transformed cells in stomach and colorectal cancers associated with colon inflammation and, although normally latent, its aberrant activation has been shown to be a common feature of epithelial-derived human cancers – including those of the gastrointestinal tract – making it a highly promising target.

TAILORED TREATMENT

The WEHI researchers are using a compound developed by the pharmaceutical company AstraZeneca called AZD1480. Once JAK kinases are switched on, they begin to phosphorylate, and consequently activate, other proteins. AZD1480 acts by binding to the JAK kinase site responsible for phosphorylation to inhibit its activity. Preclinical mouse models of gastrointestinal cancers are used in conjunction with this drug to test its efficacy. The scientists have found that AZD1480 arrests the growth of intestinal-type gastric tumours, thereby demonstrating its association with reduced STAT3 activation and increased apoptosis among tumour cells. This is a major discovery; showing for the first time that targeting excessively activated JAK kinases can suppress this class of cancers in vivo.

In order to understand the underlying mechanisms of these observations, the researchers have resorted to using a pair of human colon cancer cell lines in which the extent of aberrant activation of WNT signalling...
is different. With the AZD1480 administered they found that growth was only suppressed in those cells with excessively high levels of aberrant WNT signalling, indicating that the therapeutic targeting of the gp130/JAK/STAT3 pathway can be achieved without affecting tissue homeostasis in the gastrointestinal tract. “This observation will be important when predicting which colon cancer patients might respond best to treatment with JAK inhibitors,” explains Phesse.

These breakthrough observations will contribute significantly toward the group’s larger aim of demonstrating the efficacy of JAK inhibitors in treating human gastrointestinal tumours. They are already known to be well tolerated in humans and now, having provided the rationale for their use in gastrointestinal cancers, the group’s investigations can progress. In 2012, the team moved from the Melbourne Branch of the Ludwig Institute for Cancer Research to WEHI, and will soon be taking up laboratories in the newly established Olivia Newton-John Cancer Research Institute – a facility geared toward transferring the outcomes of laboratory research to clinical settings.

As the inaugural Scientific Director of the Olivia Newton-John Cancer Research Institute in Melbourne, Ernst, along with Buchert and Phesse, must first tackle a range of crucial issues before JAK inhibitors can be approved for use in humans with stomach or bowel cancers. Particularly important is to determine their efficacy in late-stage tumours and metastasising cancers, since these are the ones that cause the most mortality. As Ernst states, however, his team is confident that they can reproduce their encouraging results in the relevant models: “Our team is in an excellent position to bring together basic and translational cancer research in a coordinated and successful manner”. As a result of this groundbreaking research, novel therapies for gastrointestinal cancers may soon be hitting targets with a lot more accuracy.