Dr Kristen Scott forms part of a team investigating novel therapies for treating Burkitt lymphoma, a cancer of the lymphatic system. Below she highlights her lab’s key achievements and explains why she is passionate about cancer metabolism.

Your interest in cancer metabolism is extremely broad. Is it the variety of the subject that attracted you to this line of research?

The variety of mutations and alterations in metabolism that occur during the evolution from a normal cell to malignant tumour is fascinating. Even more so when you consider that cancer cells can easily adapt to environmental changes in nutrient availability, are inherently heterogeneous and change their metabolism during metastasis. It’s like an ever-changing puzzle, which you think you’ve solved, only to find out that a critical piece is missing and tantalisingly just out of reach. I’m excited to be part of the scientific community that tries to solve these puzzles and advance knowledge on how to detect and treat the metabolic aspects of cancer.

Can you provide an overview of the fat-producing pathways in cancer cells and explain how this process varies for different types of cancer?

Cancer cells alter their metabolism to quickly process sugar and amino acids for energy. This requires minimal oxygen and is akin to yeast fermentation of sugar into alcohol. This altered metabolism, the Warburg effect, is named after Otto Warburg who discovered the phenomenon in the 1920s and, some 100 years later, is now considered a hallmark of cancer. This increased consumption of sugar and amino acids provides an abundance of carbon and cofactors for cancer cells to make fatty acids, which are necessary for the cancer cell to grow and divide. The carbon precursor source varies between cancers and some cancers also bring in fatty acids from the surrounding environment to help meet their needs. Regardless of the source of carbon, the fatty acid synthesis pathway is important for the cancer cells to survive.

In what ways could the treatment of cancer be improved through a better understanding of these pathways?

By understanding the fundamental metabolic requirements of cancer cells, we can identify new vulnerabilities to exploit for cancer therapy. We can use these findings to design new multi-modality therapy regimens that augment traditional chemotherapy, sensitize cancer cells to radiotherapy and provide second and third line options for treating refractory cancers. Exploiting the metabolic requirements of cancer has been especially important in advancing the field of imaging cancer and is the basis of why positron emission tomography (PET) scans are very helpful in identifying cancerous masses and responses to certain therapies.

MYC gene’s function of catabolic programme regulation is well established. Why has it proven difficult to observe how MYC influences fat regulation?

It has been known for some time that the fatty acid synthesis pathway is dysregulated in cancer at several different levels. In many types of cancer, transcription of lipogenic genes is mediated by a transcription factor called sterol regulatory element-binding proteins (SREBP). This transcription factor is downstream of several oncogenic pathways, which vary depending on the type of cancer investigated. The idea that MYC would also contribute to the regulation of fat production had simply not been considered. While we have found that MYC does, in fact, transcriptionally activate fatty acid synthesis, this phenomenon may be isolated to cancers in which MYC is driving transformation. However, this does not detract from the important role fatty acid synthesis plays in tumorigenesis and progression in a wide array of cancer types.

What have been your key achievements toward identifying metabolic pathways in MYC-driven lymphoma and what do your results signify?

The seminal finding of our studies has been to demonstrate that disabling the regulatory node of fatty acid synthesis, acetyl-CoA carboxylase, whether by drug treatment or genetic manipulation, results in cancer-
A group of researchers at Moffitt Cancer Center in Florida is investigating cancer metabolism to improve understanding of the disease. One of the team’s main programmes of research is determining ways to stifle fat producing pathways, to limit the progression of tumours.

Targeting pathways: an effective path to mitigating cancer

CANCER IS A general term used to group a large number of diseases that are characterised by uncontrolled growth and can affect any tissue in the body. Worldwide, it is a leading cause of morbidity and mortality, and is responsible for millions of death each year. Cancer is caused by accumulating alterations in normal cells that eventually transform them into to a rapidly dividing tumour cell, typically progressing from a pre-cancerous lesion to malignant tumours.

Cancer cells are incredibly adaptable and can survive and proliferate under extraordinary conditions that block the growth of normal cells. This knowledge has contributed to a wider understanding within the cancer research field that has, over time, led to the development of a new field known as cancer metabolism.

FIELD OF POTENTIAL
In 1924, the renowned biochemist Otto Warburg postulated a theory concerning what he believed was a fundamental difference between normal cells and the rapid proliferation of cancer cells. He suggested there were crucial metabolic differences between the two types of cells and it was this change in metabolism that was a fundamental cause of cancer. He described how cancerous cells consumed glucose and produced lactic acid under aerobic conditions. However, for nearly 80 years it was unclear if this occurs as a result of cancer, or was, in fact, the cause for it.

More recently, research has shown that cancer cells can develop extremely efficient processes to consume and utilise nutrients. Indeed, it has been demonstrated that cancerous cells alter their metabolism to process sugars, fats, amino acids and other sources of energy as a fuel for continuous proliferation. As a result, researchers now have an appreciation for these altered metabolic processes; of how they drive specific cell death and a significant delay in tumour progression.

Our studies suggest that targeting fatty acid synthesis represents an exciting new type of therapy for B-cell lymphoma and other malignancies that have MYC involvement. This research has led to new collaborations, where we are developing imaging techniques and new drugs targeting this aspect of cancer metabolism.

Finally, what other projects are you currently involved with?

Cancer cells catabolise a lot of sugar and most of it leaves the cell as lactate. This is a key feature of the Warburg effect and our lab is actively trying to understand the implications of blocking lactate export on the cancer cells themselves, the surrounding supporting cells and on the host in general.

I am also involved in work to support host metabolism to fight cancer cachexia in patients, which is the wasting of fat and muscle stores and is a particularly devastating side effect of cancer growth.

www.internationalinnovation.com
the growth of tumours rather than being a consequence of their aberrant growth.

**POTENTIAL PROLIFERATION PREVENTIVES**

These findings have proven essential to progress within the field of cancer metabolism and are the inspiration for several research endeavours underway at the Moffitt Cancer Center, USA. Under the guidance of Dr John Cleveland, Dr Kristen Scott forms part of a team focused on Burkitt lymphoma (BL), an extremely aggressive form of non-Hodgkin’s B-cell lymphoma.

A hallmark of BL is the unchecked expression of c-MYC (MYC), an oncogenic transcription factor that is activated in over half of all human tumour types. MYC controls many of the pathways that cells need for growth, and, in cancer, MYC directs the switch from oxidative phosphorylation to aerobic glycolysis to get energy from sugar (the Warburg effect).

An essential requirement for a cell to divide and produce two daughter cells is the production of new membranes. This intracellular process, where proteins and lipids help form the cell membrane, places high demands on the synthesis of fatty acids. As the understanding of the chain of events involved in the development of cell proliferation has evolved, so too has the development of potential ways to disable this process. By identifying the crucial role that fatty acid synthesis plays in the tumorigenesis of BL, Scott and her team have uncovered a means of blocking fatty acid synthesis.

**THE KEY – CONTROLLING EXPRESSION**

It is known that two key enzymes regulate the synthesis of fatty acids. These are called acetyl-CoA carboxylase 1 (ACC1) and fatty acid synthase (FASN). While the former is responsible for catalysing the carboxylation of acetyl-CoA to malonyl-CoA (and is the most tightly regulated step in the entire pathway), the latter directs the synthesis of the fatty acids.

In the majority of normal tissues, ACC1 and FASN are expressed at very low levels, but both are upregulated in several solid tumour types. Indeed, the increase in their expression has been shown to correlate with poor outcomes in some malignancies. Thus, controlling the expression of ACC1 and FASN is crucially important in improving treatment efficacy of B-lymphomas with MYC involvement.

**TARGETED FOCUS**

MYC specifically binds to short sequences of DNA called E-boxes to regulate the expression of its targets. Scott and her team have shown that MYC binds to E-boxes present in the ACC1 and FASN promoters and induces their transcription. This led the researchers to consider that both ACC1 and FASN are targets for MYC, suggesting that ACC1-directed production of fatty acids (lipogenesis) is a vulnerability for tumours involving MYC.

The team showed that inhibiting ACC1 blocked lymphoma cell growth and actually led to rapid cell death. From this, Scott and her colleagues surmised that fatty acid synthesis was required for BL to survive. Importantly, it was noted that healthy B-cells are not sensitive to the inhibition of ACC1, meaning that agents that target ACC1 could prove an effective strategy for selectively killing B-cell lymphoma.

MYC is implicated in several types of cancer. Thus, targeting ACC1 may be a general means to prevent and treat many malignancies. Ultimately, this novel study of cancer metabolism has placed a new focus on targeting specific pathways in cancer, unearthing novel therapies to be further explored in the future.