Commentary: Richard Goodfellow

Citrullination – linking cancer and autoimmunity?

Not many people had heard about protein citrullination until Padlock Therapeutics was acquired by Bristol-Myers Squibb Company in April for up to $600 million. This 2014 start-up is now set to deliver a 30-fold return to its founding investors if all the development and regulatory milestones are achieved. And all of this in the space of two years.

This staggeringly fast exit was based on understanding the role of peptidyl arginine deiminases (PADs) in driving antigenic citrullination in rheumatoid arthritis (RA) and other autoimmune conditions. The scientific approach can be summarised as follows: autoimmune disease is caused by citrullinated antigens and blocking the PAD enzymes that cause this modification will ameliorate the pathology. All previous attempts to treat RA have been focused on blocking inflammatory mediators circulating in the body rather than blocking the cause of their production. In other words, instead of dousing the flames Padlock set out to stop fuelling the sparks.

But if Scancell is right, this novel pathway could also hold the key to controlling cancer. Our immunotherapy platform called Moditope is based on exploiting the normal immune response to stressed cells, which is largely mediated by cytotoxic CD4+ T cells, and harnessing this mechanism to eradicate tumour cells. Citrullination holds the key.

It works like this. Cancerous cells undergo autophagy due to stress caused by the lack of oxygen and nutrients, and they then digest and modify some of their own proteins. They do this by using PAD enzymes, which are presented as citrullinated peptides on the cell surface. The immune system detects these modified peptides and sends activated T cells around the body to search out and destroy the cancerous cells that are expressing these peptides. However, as the tumour environment is immunosuppressive, T cells are inhibited and the tumour cells continue to grow and metastasise. Scancell has overcome this limitation and shown that treatment with certain citrullinated peptides can expand the activated T cell population to such an extent that the immunosuppressive tumour environment is reversed and tumours are eradicated.

This novel approach has many potential advantages. For example, once the activated T cell population has triggered the immune response at the tumour site, the effect will be amplified; therefore our therapy should even be effective against late-stage tumours. Our technology has the ability to release the "brakes" that cancer cells have evolved to evade detection; therefore, there may be no need to add checkpoint inhibitors to allow the T cells to do their job. Finally, and importantly, normal healthy cells do not digest and modify their own proteins which bodes well for the safety of immunotherapies designed with our technology.

Although many proteins can be citrullinated, the best targets for cancer immunotherapies developed with our technology appear to be the cytoskeletal and abundant cytoplasmic proteins, which are preferentially digested during autophagy. One such protein is vimentin, which is the major cytoskeletal protein found in mesenchymal cells. All mesenchymal tumours such as sarcomas, melanomas and lymphomas express vimentin as their major cytoskeletal protein and are therefore potential targets for citrullinated vimentin immunotherapy. In addition, many epithelial tumours switch from expression of cytokeratin to vimentin during metastasis in a process called epithelial mesenchymal transition (EMT).

This change in phenotype enables the cell to become mobile and metastasise to new locations in the body. Most solid tumours, including lung, breast, ovarian, endometrial, gastrointestinal and prostate tumours, also undergo EMT and switch to the expression of vimentin. Alpha-enolase, a glycolytic enzyme, is upregulated in many cancers including breast, ovarian, pancreatic ductal carcinoma, lung cancer and liver cancer, to provide energy for their rapid proliferation. As one of the most abundant cytoplasmic proteins, it is a major substrate for autophagy and is citrullinated. So the incorporation of citrullinated vimentin and alpha-enolase peptides into a therapeutic using our technology has the potential to treat many different forms of cancer.

Pre-clinical results appear to confirm this hypothesis. A single immunisation with citrullinated peptides from vimentin and alpha-enolase induced potent CD4+ T cells, potent anti-tumour activity and long-term survival in 100% of animals with no associated toxicity. These exciting results show how CD4+ T cells can mediate potent antitumour responses against citrullinated epitopes on tumour cells and illustrate for the first time how citrullinated peptides produced during autophagy may offer especially attractive targets for cancer therapy.

Scancell's lead product, Modi-1, which contains two citrullinated vimentin epitopes and one citrullinated alpha-enolase epitope, is expected to enter clinical trials in 2017.

Of course a pathway connecting two diseases might be expected to influence both in certain circumstances. Indeed, there is some epidemiological evidence to suggest that certain cancers are less common in patients with RA. Furthermore, there could be a risk of exacerbating autoimmune conditions during treatment with such immunotherapies. However, no toxicity has been observed to date.

Most of the exciting and disease transforming advances in recent years have been driven by a new understanding of the biology behind the disease. With protein citrullination, two companies have independently discovered and developed solutions for the treatment of two different diseases based upon a common pathway and connected via the immune system. Both Scancell and Padlock, through the application of science and by thinking differently, could transform the way in which we understand the treatment of cancer and autoimmune disease.

This article was written by Dr Richard Goodfellow, joint chief executive officer of Scancell Holdings Plc in the UK.