Potential leukaemia drug could be a good BET

October 2 2011, by Kat Arney, Cancer Research UK

(Medical Xpress) -- A team led by Cancer Research UK scientists in Cambridge have made a significant discovery in the lab that could lead to a new treatment for leukaemia.

Writing in the scientific journal *Nature*, the scientists show that a chemical called I-BET151 can kill leukaemia cells grown in the lab and effectively treat mice with the disease. And although it's still quite early days, the researchers hope that the potential new drug will be heading into clinical trials as soon as possible.

As well as these impressive results, the other thing that makes this new development so exciting is the way that I-BET151 works.

Here's a short video featuring lead researchers Professor Tony Kouzarides and Dr Brian Huntly, talking about their discovery and what it might mean for people with leukaemia:

The MLL challenge

The researchers, led by Professor Tony Kouzarides, Dr Brian Huntly and Dr Mark Dawson, set their sights on type of cancer called mixed lineage leukaemia (MLL), previously thought to be a form of acute lymphoblastic leukaemia but now believed to be a separate condition. MLL is the most common type of leukaemia in children under 2 years old and accounts for up to one in 10 cases of leukaemia in adults.

Although survival from leukaemia has increased significantly in recent years, this particular form of the disease has remained stubbornly difficult to treat and often comes back after therapy. So we urgently need new approaches for tackling it.

One of the reasons the disease is so aggressive is the presence of unusual molecules called 'MLL fusion proteins' in cancer cells. These are produced when part of the gene encoding the instructions to make a protein called MLL accidentally gets stuck next to another gene (somewhat confusingly, the gene has the same name as the disease).

The MLL protein normally plays an important role in producing blood cells by switching specific genes on at certain times, as and when they're needed. But unlike the well-behaved, healthy version of the protein, MLL fusion proteins run amok, turning on a bunch of inappropriate genes that drive the growth of leukaemia cells.

The scientists figured that stopping MLL fusion proteins from switching these genes on might stop the cancer from growing. But first, they had to understand exactly how the fusion proteins were working, in order to find the best target to hit with a potential treatment.

Using cutting-edge protein analysis techniques, researchers in Professor Kouzarides' lab rummaged around inside cells to identify groups of proteins that work together to switch genes on. Intriguingly, they found that members of a family of proteins – known collectively as BET proteins – were often associated with MLL fusion proteins. But what were they doing?

BET and histones – the missing link

The Cambridge team realised that BET proteins were acting as a 'missing link' between MLL fusion proteins and the genes they switch

on. In order to explain how this works, we need to go into a bit of scientific detail about how genes get turned on.

Genes are biological instructions encoded within DNA – long strings of chemical 'letters' that make up the blueprint of life in all our cells. But DNA isn't allowed to float around freely inside a cell, as it would get hopelessly tangled. To prevent this, DNA is carefully wound around ball-shaped proteins called histones to form a structure called chromatin – the effect is a little bit like a necklace of beads on a string.

Not only are histones important for keeping DNA organised, they also play a vital role in helping a cell to know which genes should be switched on or off through special chemical 'tags', known as histone modifications. These chromatin tags are often referred to as 'epigenetic' modifications, because they provide information in addition to the genetic code found in DNA. Some of these modifications attract proteins that turn genes on, while others recruit proteins that shut them down.

In this case, the researchers knew that certain histone modifications (known as acetylated lysine) were very attractive to BET proteins. Not only that, but the BET proteins brought along MLL fusion proteins, which can switch on genes that drive leukaemia.

This explains how MLL fusion proteins and BET proteins were acting together to switch on the genes that drive leukaemia. The challenge was to figure out how to stop them.

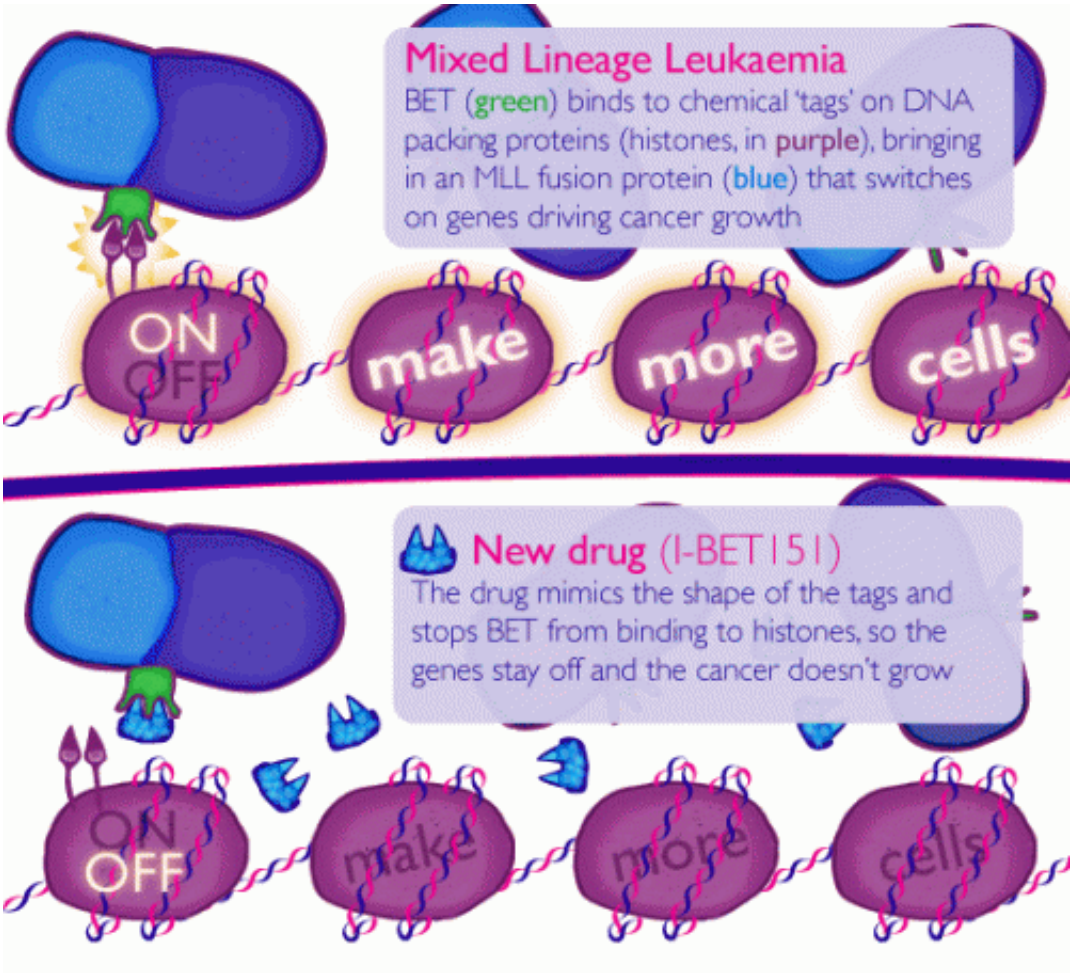
Introducing I-BET151

To do this, the researchers turned to a molecule called I-BET151, developed by the drug company Glaxo Smithkline. This chemical sticks to the same part of the BET proteins that recognise histone

modifications, and prevents them from attaching to chromatin.

The researchers reasoned that, if the drug could stops BET proteins from binding to chromatin, it ought to stop them from bringing in MLL fusion proteins. And because MLL fusion proteins aren't being brought in, the leukaemia genes don't get switched on.

Here's a diagram to explain what's going on:



To find out whether I-BET151 worked as well in practice as it should in theory, the researchers teamed up with Dr Huntly and his colleagues, who are experts in blood cancers.

First the scientists tested the chemical on human leukaemia cells growing in the lab, with impressive results. The cancer cells stopped growing and started dying. And when they tested I-BET151 in mice with MLL, the results were just as dramatic.

After 40 days, more than 60 per cent of the animals given I-BET151 were still alive. And in mice with a more established, aggressive form of the disease, the drug was still remarkably effective, with the animals given I-BET151 surviving much longer than those given a dummy (placebo) treatment.

Why is this important?

It's important to stress that these are still early experiments and the chemical is not quite ready to be tested in MLL patients yet. But the researchers are optimistic that clinical trials are on the cards in the not-too-distant future.

But there are a couple of other important points to note about this research. For a start, I-BET151 works in an entirely different way to other cancer drugs.

Most therapies either target proteins inside or on the surface of a cancer cell, or directly attack DNA. This is the first cancer drug designed to target specific epigenetic modifications and affect the activity of a particular set of genes.

There are some experimental cancer drugs (such as azacitidine) which can affect certain epigenetic modifications, but these have a much less

precise effect. To use an analogy, I-BET151 is like a sniper's bullet while drugs like azacitidine are a scattergun.

By proving that an approach like this can work against MLL in the lab, the researchers have opened the door to the possibility that I-BET151 – or drugs like it – might work against other types of cancer too.

It's also worth pointing out that this is a nice demonstration of the importance of collaboration between scientists and clinicians in developing new cancer treatments – something that we're hoping to encourage through our network of Cancer Research UK Centres.

Finally, it's important to highlight that this is the culmination of many years of detailed lab research into epigenetic modifications and gene activity. It takes time to translate fundamental discoveries about the nature of cancer cells into new treatments for patients, and we have funded Professor Kouzarides and his team since the early 1990s.

This kind of long-term funding into basic biological research is vital if we are to continue making progress in beating cancer in the future.

More information: Dawson et al, Inhibition of BET recruitment to chromatin as an effective treatment for MLL-fusion leukaemia, *Nature* (2011) DOI: 10.1038/nature10509

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