New approach to treating arthritis and other inflammatory diseases

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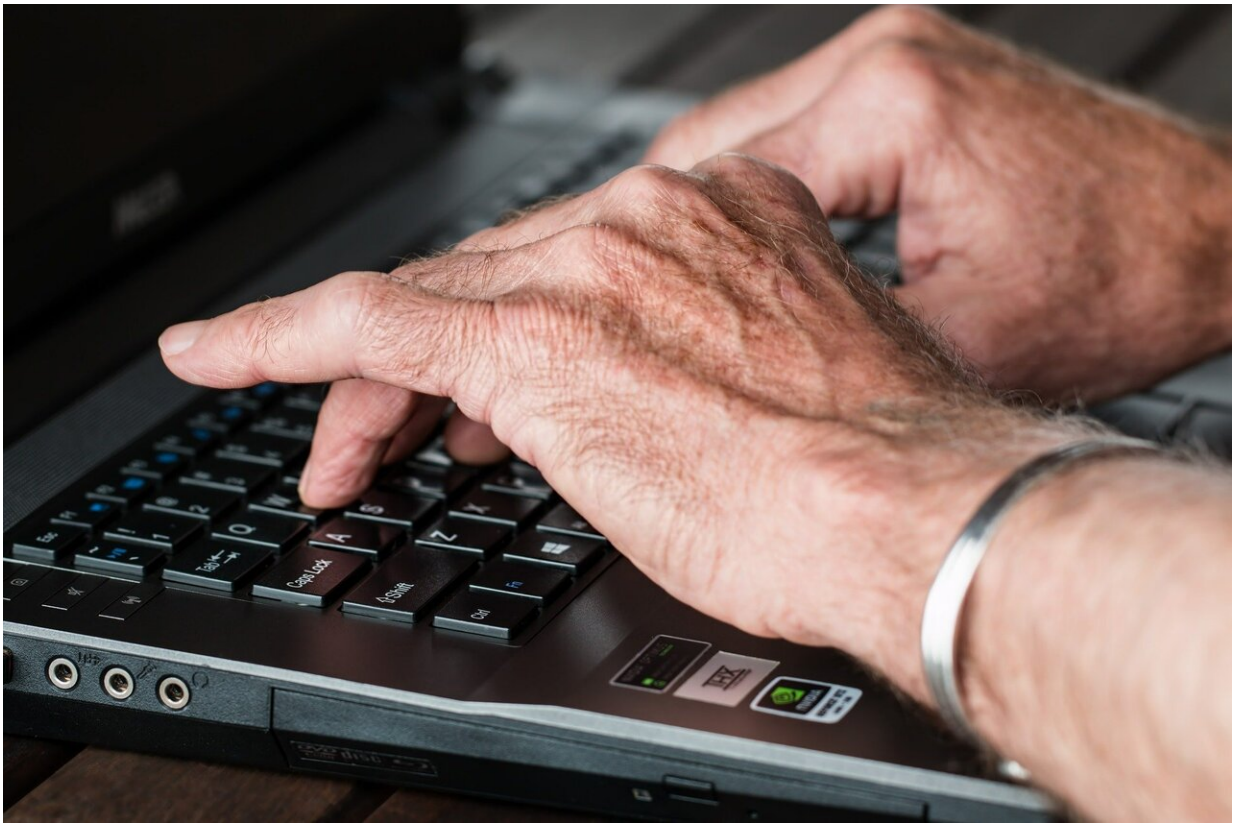

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Researchers from Peter Mac have discovered an innovative way to dampen severe inflammation in mice, uncovering a potential new therapeutic approach for inflammatory and autoimmune conditions such

as arthritis, psoriasis and liver disease, as well as some cancers.

The research, co-led by Prof Mark Dawson's laboratory, in collaboration with scientists from at GlaxoSmithKline (GSK), made the discovery while looking for new ways to improve an existing anti-cancer therapy that interferes with processes controlling gene expression inside cells.

Hyperactive cells in cancer and autoimmune diseases often express abnormally high levels of certain genes that drive the disease. Therapies that can reverse this abnormal gene expression have shown benefit in both cancer and inflammatory conditions.

However, because these processes are also required in normal cells many of these therapies have unwanted side effects, prompting researchers to modify the drug design which led to the development of compounds that are far more specific than their predecessor.

"The findings actually came as quite a surprise," says study lead author Dr. Omer Gilan.

"For the purpose of advancing research the GSK medicinal chemistry team originally designed these new series of compounds in an attempt to improve on an existing cancer therapy. We weren't really focused on inflammation in the beginning."

The team were working on a class of drug that shuts down the action of the BET family of proteins, which are currently being evaluated in clinical trials for a variety of cancers across the world.

These drugs work by blocking two sites within BET proteins, rendering the proteins non-functional and killing the cancer cells.

While this therapeutic approach can be effective, it can also lead to some

unwanted side effects.

The researchers wanted to determine if they could minimise off-targets effects whilst maintaining anti-cancer activity. To do this, they worked with the team of scientists at GSK who designed compounds to interfere with just one of the sites at a time.

To their surprise, they discovered that when they selectively blocked the second BD2 site the drug no longer had anti-cancer activity but became a potent suppressor of immune cell function.

"When the selective BD2 blocker was given to mice with inflammatory conditions that mimic human auto-immune diseases including arthritis, psoriasis and liver disease, it acted to suppress immune function in a potent and specific way," says Dr. Gilan.

The treatment was well tolerated by the mice and their inflammatory disease was vastly improved and in some cases was even more effective than currently available treatments.

"Another really great outcome of this study is that we have also finally shed light on the biological mystery of why these BET proteins have two almost-identical regions that are conserved throughout evolution. Importantly, by showing that each region has a completely distinct and non-redundant role, we have discovered an entirely new approach to tackling diseases such as cancer and inflammation" explains senior author on the study, Prof Mark Dawson.

If confirmed in humans, the findings could have a major impact on people suffering from both malignant and inflammatory diseases in Australia and around the world.

"We are still a way off testing this new therapy in humans, but the proof

of principle studies in mice are certainly promising," says Prof Dawson.

The paper entitled "Selective targeting of BD1 and BD2 of the BET proteins in cancer and immune-inflammation" was published in the journal *Science*.

More information: Omer Gilan et al. Selective targeting of BD1 and BD2 of the BET proteins in cancer and immuno-inflammation, *Science* (2020). DOI: 10.1126/science.aaz8455

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