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Insights into how TB tricks the immune system could help combat the disease

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Researchers have identified a potential way to manipulate the immune system to improve its ability to fight off tuberculosis (TB).

TB is a major problem for both humans and cattle and the new findings could help scientists to create better drugs to combat the disease in both.

The disease is caused by the bacterium *Mycobacterium tuberculosis*, which infects the lungs. The mycobacteria are able to establish persistent TB infections by taking up residence in macrophages – cells of the immune system that would normally destroy invading microorganisms.

Now, in early stage research published in the *Journal of Biological Chemistry*, researchers from Imperial College London and Stanford University have revealed precisely how unusual sugars on the surface of the mycobacteria that cause TB are able to latch onto the macrophages and disarm them. They now hope that scientists at Imperial and elsewhere can use this knowledge to develop small molecule drugs that latch tightly onto the same site.

These drugs could potentially fight tuberculosis in a number of ways, say the researchers. They could create a barrier to prevent the mycobacteria from attaching to the macrophages; they could transport drugs to kill the mycobacteria; or they could change how the macrophages behave, so that they destroy the mycobacteria rather than harbouring them.

Professor Kurt Drickamer, a lead author of the research from the

Department of Life Sciences at Imperial College London, said: "TB is hard to fight effectively because it can hide inside the cells of the immune system that should be able to destroy it. We were surprised to find that there is an extensive interaction between the macrophage and one particular type of molecule on the surface of the mycobacteria. The nature of the interaction gives us hope that we can make simple molecules that block the ability of the mycobacteria to subvert the macrophages."

The new insights into how macrophages can be switched on and off could also be used to develop better vaccines against a range of conditions, such as HIV, say the researchers. Vaccines need to generate a response from the immune system in order to be effective, but researchers have struggled to find ways of generating a sufficiently strong reaction.

Many vaccines for animals use mycobacteria to attract macrophages, but this approach is considered to be too toxic to be used in humans. The researchers are hopeful that if small molecules can be developed that trigger a response from the macrophages in the way that they envisage, these molecules could be used in vaccines to wake up the immune system without toxic side-effects.

Research co-author Dr Maureen Taylor, also from Imperial's Department of Life Sciences, added: "The problem of how to spark a response from the immune system has proved to be a major hurdle for the development of vaccines against a range of diseases. We think that scientists may be able to overcome this by using the new, simpler molecules that we discuss in our research. This idea is currently at an early stage but we are looking forward to exploring it further."

More information: "Mechanism for Recognition of an Unusual Mycobacterial, Glycolipid by the Macrophage Receptor Mincle" *Journal*

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of Biological Chemistry, Hadar Feinberg, Sabine A. F. Jégouzo, Thomas J. W. Rowntree, Yue Guan, Matthew A. Brash, Maureen E. Taylor, William I. Weis, and Kurt Drickamer

Provided by Imperial College London

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