Every year, over two million people worldwide still die from tuberculosis (TB). TB is a serious public health threat worldwide, due to an alarming increase in the rates of Mycobacterium tuberculosis strains that are resistant to current drug treatments.

In May 2013, Dr Sanjib Bhakta published a study in the British Medical Journal, which looked at whether common medicines, such as ibuprofen, could play a role in the development of new anti-TB drug treatments.

The disease is difficult to treat, because patients need to follow at least a six-month daily course of chemotherapy, and in cases of multi-drug-resistant strains, effective treatment can take up to two years. Failure to complete the full course leads to increasingly drug-resistant strains of the disease developing.

There are now several strains that are multi-drug resistant – and a few defined as being totally drug resistant, meaning that treatment with current therapies is not possible. No new antibiotics have been developed since the 1960s, and TB treatments have focused on new combinations of the existing drugs.

Dr Bhakta said: “Efforts to develop new drug compounds have not yet been successful. As a result, there has recently been a renewed interest in re-purposing existing drugs for the treatment of infectious diseases. This also offers the advantage that we already have information about their pharmacological profiles and safety for use in humans, which can save time and resources in developing treatments which can safely be delivered to patients on a large scale.”

Dr Bhakta and his research group used an innovative screening technique known as the HT-SPOTi technique, which was developed by the Mycobacteria Research Laboratory, to assess whether ibuprofen and its chemical analogues were effective at attacking the TB pathogen. They tested a number of over-the-counter non-steroidal anti-inflammatory drugs (NSAIDs), including ibuprofen, carprofen (currently used in veterinary medicine) and a synthetic derivative of ibuprofen. Dr Bhakta has described this group of drugs as “one of the safest over-the-counter drugs available – including for children.”

The research team tested the ibuprofen and other compounds against replicating, non-replicating and drug-resistant forms of the TB-causing bacteria grown in vitro. In vitro testing provides the bacteria with optimum growth conditions, without the immune responses that would be provoked by a host cell infection. The results showed for the first time that ibuprofen, carprofen and the ibuprofen derivative were all effective at specifically killing the TB pathogen.

“Other research groups have shown that these compounds are also effective at treating TB in mice,” said Dr Bhakta. “However, in vitro testing enables us to focus on endogenous mechanisms of action of this group of over-the-counter medicines that exist within the TB pathogen.”

By targeting several types of bacterial pathogens, including TB, with the same compounds, the team was able to ascertain that the antibiotic properties displayed by ibuprofen and the other compounds are specifically anti-TB, rather than being effective against a broad spectrum of bacteria.

Using an interdisciplinary approach, the research team now hopes to identify the specific molecular target within the TB pathogen that the compounds interact with, and the biological process which it interrupts in order to inhibit the pathogen’s growth. In further tests, the team found that administering ibuprofen and its analogues in combination with existing antibiotics provoked an even higher death rate in the bacteria than if either of the drugs were used alone, opening up the possibility of new combination therapies for TB.

The team also found that ibuprofen and its analogues could successfully target both active and dormant TB cells. Dr Bhakta added: “When in the active state, TB bacteria are multiplying within the host and causing disease – and this is the state when treatment is normally initiated. In around 70% of all TB infection cases, the host cells spontaneously heal in response to initial invasion by the pathogen. In 90% of the remaining cases, a complex host immune response triggers the TB pathogen to enter a dormant state, in which cells do not multiply, but remain fully viable. Around one-third of the world’s population is believed to carry the dormant TB bacteria – and these can become active at any time. Therefore, developing treatments for dormant TB would eliminate the chances of regular reactivation cases reported worldwide and is an exciting area for further investigation.”

With TB cases in the UK now almost on a par with levels in the whole of the US, at around 9,000 new cases per year, controlling TB infections represents a pressing challenge for both the UK government and international health bodies such as the World Health Organization, which issues regular reports on global infections.

Dr Bhakta and his team’s work represents an important new avenue of research, which will further our understanding of this global killer, and might well lead to effective new treatments that could save millions of lives.

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