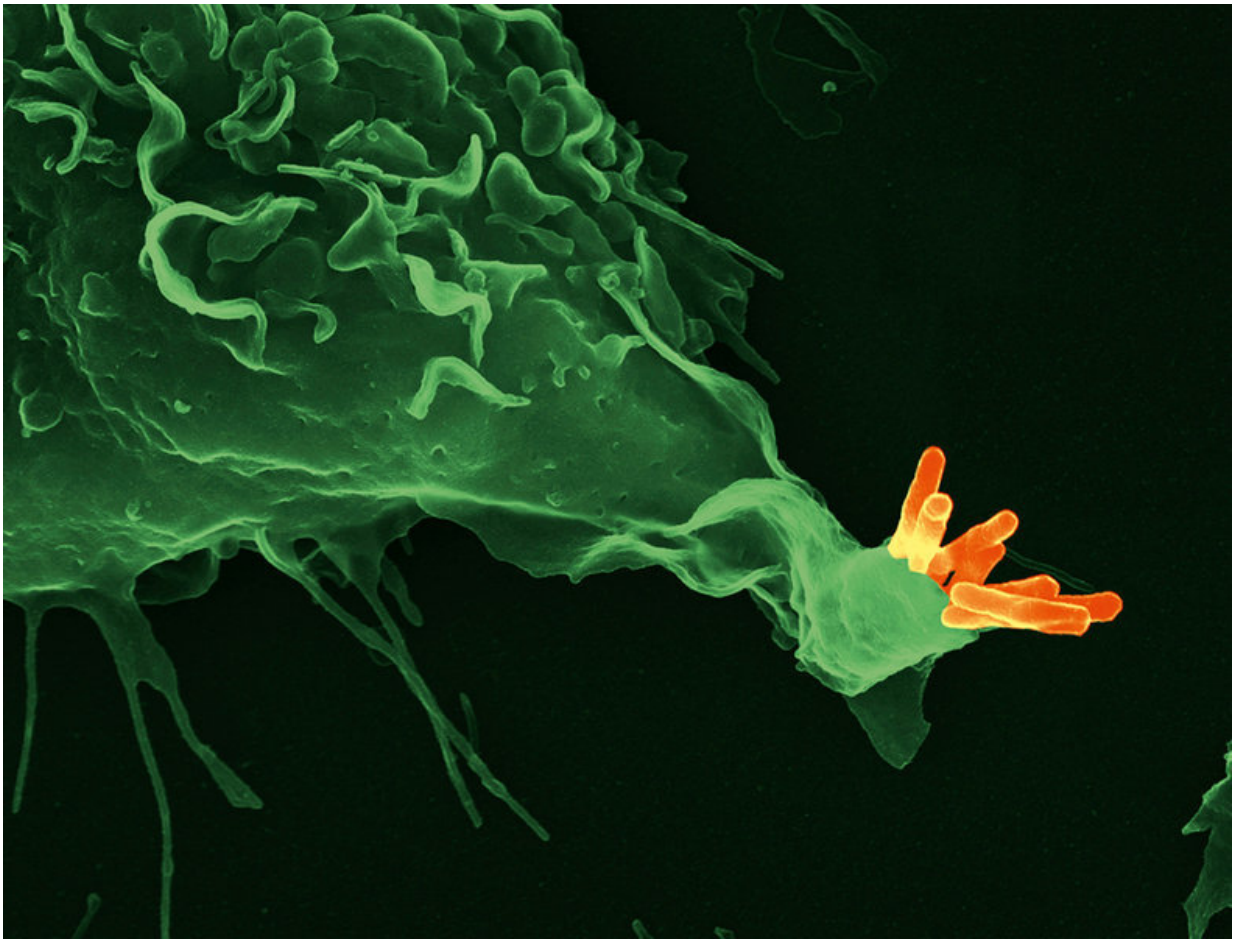
# Activity of two genes able to predict active tuberculosis

April 9 2018



A phagocyte a specialized white blood cell (green), is about to trap and digest tuberculosis bacteria (orange). Protected by a particularly resistant cell wall, however, the pathogens can survive for years in the macrophages and be released again if the immune system is weakened. Credit: Max Planck Society

The closer the contact someone has with individuals with tuberculosis, the more likely they are to become infected with the pathogen. However, only about five to ten percent of people infected with the pathogen go on to develop the disease. An international team of researchers, including scientists from the Max Planck Institute for Infection Biology in Berlin, has now developed a simple blood test to enable them to estimate the risk of developing active tuberculosis. Using the new test, the researchers can predict who is likely to come down with the disease. The test measures the activity of pairs of genes involved in the inflammatory response. This should in future enable doctors to offer prophylactic antibiotic treatment to people at high risk of going on to develop active disease, and conversely to avoid unnecessarily treating people who are at low risk.

Active tuberculosis remains one of the most feared diseases in the world today. The active disease causes terrible suffering. Early treatment is therefore highly desirable. The disease is only spread by people suffering from the active disease, and not by healthy people with a latent infection. Prophylactic treatment before the disease even manifests would therefore not only reduce suffering for those developing the disease, it would also reduce its spread. Tuberculosis treatment can, however, have serious side effects. Consequently, it is not possible to simply offer prophylactic antibiotic treatment to all affected with latent tuberculosis.

A test able to predict the risk of developing active tuberculosis would offer a solution to this problem – people at high risk could be offered prophylaxis, while people at low risk could be spared the potential side effects.

In a new study, researchers analyzed the health status of around 4,500 people from South Africa, the Gambia and Ethiopia living with a tuberculosis patient. The researchers measured the amount of various RNA molecules – and thus the activity of the corresponding genes – in

blood cells. Using sophisticated software, they identified genes which are more active or less active in individuals who subsequently go on to develop active tuberculosis than in people who remain healthy. They then paired up sets of one up-regulated and one down-regulated gene and calculated the predictive power of these pairs.


In future, molecules from blood samples can tell physicians if somebody will develop tuberculosis. Credit: MPG/ J. Steengard

## Risk gene for active tuberculosis

They then looked at household contacts of people with tuberculosis and compared 79 people who developed active tuberculosis within the

following two years with 328 healthy people who did not go on to develop the active disease. They found differences in activity of two gene pairs between the two groups. Importantly, these differences were not dependent on where they were from. "Using the pattern of activity of these 'risk 4' genes, we were able to determine the tuberculosis risk of infected individuals. That means we can say one year earlier who is likely to develop active tuberculosis," explains Kaufmann. Because the study focussed on individuals from various regions across Africa, the test should be applicable across the whole of the continent.

The results show that certain gene pairs can predict tuberculosis risk. With just a single pair, the researchers were able to identify most of those who would go on to develop active tuberculosis. By adding in a second gene pair, the predictive power of the gene analysis was improved further. "These results are the most significant findings so far in our ten-year Grand Challenges project," says Stefan Kaufmann from the Max Planck Institute for Infection Biology. The Grand Challenges project, which was supported by the Bill & Melinda Gates Foundation, involved close collaboration between seven research groups from Africa, Europe and the USA. Kaufmann was responsible for coordinating the project. "This study proves, not only that a partnership between North and South can work, but that such a partnership can also make a significant contribution to controlling one of the most terrible diseases on the planet," says Kaufmann.

Based on these results, there are now plans to develop, in conjunction with a commercial partner, a test suitable for practical use on the ground. This could provide much more accurate results than the diagnostic tests currently available, and also enable doctors to select and offer prophylactic antibiotics to those patients most likely to develop active tuberculosis. At the same time, it could help doctors to avoid subjecting individuals who would not go on to develop the disease to the risks associated with several weeks of antibiotic prophylaxis.

**More information:** Sara Suliman et al. Four-gene Pan-African Blood Signature Predicts Progression to Tuberculosis, *American Journal of Respiratory and Critical Care Medicine* (2018). DOI: 10.1164/rccm.201711-2340OC

Provided by Max Planck Society