

# Cystic Fibrosis Research News

## Title:

Lymphocyte responses to *Mycobacterium tuberculosis* and *Mycobacterium bovis* are similar between BCG-vaccinated patients with cystic fibrosis and healthy controls

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## What was your research question?

We wanted to know if the defense reactions (immune responses) of people with CF seen at the Campinas CF Reference Center (CERFC, Campinas, Brazil) against *Mycobacterium tuberculosis* and *Mycobacterium bovis* have similar intensity in comparison with healthy individuals in terms of white blood cell (lymphocyte) production.

## Why is this important?

Nontuberculous mycobacteria (NTM) have become a worrisome group of bacteria in some CF centers in Europe and the United States. Unexpectedly, only a low frequency of NTM was observed at CERFC and we think this is explained by the Bacille Calmette-Guérin (BCG) vaccination, which is routinely applied in Brazilian (babies) for tuberculosis prevention and can cross-react with NTM.

## What did you do?

White blood cells (lymphocytes) of 10 patients with CF and 10 healthy controls were cultured and stimulated with specific bacterial proteins of *M. tuberculosis* and *M. bovis* (BCG), and with the unspecific stimulant Phytohemagglutinin (PHA) (a positive control used to generate an immune response with which to compare the bacterial treatments), for six days. After this, we measured the activation of lymphocytes (expressed as the Lymphocyte Proliferation Index, LPI), which is indicative of response to both microorganisms. As the immune system produces different types of lymphocytes, with different functions, we also investigated which were the most frequent lymphocyte types in the response against the microorganisms studied here. The lymphocyte types we studied were: CD4 T cells, also known as helper T cells,

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as they help other immune cells to kill the invading microorganisms; CD8 T cells, also known as cytotoxic T cells, as they kill the cells that are infected with the invading microorganism; Gamma-Delta (GD) T cells, which have similar functions to both CD4 and CD8 T cells, but recognize a restrict group of proteins produced by invading microorganisms; and CD19 cells – the B cells – which produce antibodies against invading microorganisms.

## What did you find?

People with CF had similar LPIs, that is, similar intensity in the lymphocyte production, in comparison with healthy controls, against both *M. tuberculosis* and BCG. The most frequent lymphocyte type produced by both patients and controls were CD4 (helper) T cells, which were significantly higher in number than cytotoxic (CD8) and gamma-delta (GD) T cells, and B cells, in both groups. However, while the pattern of response was similar between CF and healthy people, people with CF produced significantly more CD8 T cells than GD and B cells against both *M. tuberculosis* and BCG, while healthy controls produced more B cells than CD8 and GD T cells against both microorganisms. Further, CF patients also tended to produce more cytotoxic (CD8) T cells when their white blood cells were stimulated with the positive control PHA.

## What does this mean and reason for caution?

The lymphocyte response against *M. tuberculosis* and BCG is probably a memory response of the host immune system driven by the BCG vaccination and it may cross-react with NTM, which, in turn, may explain the low NTM bacterial frequency in our center. We did expect a higher response of CD4 (helper) T cells, as they are the main cells involved in the adaptive response against mycobacteria. The difference between CF patients and controls regarding CD8 T cell activity, although not significant, is intriguing. Tuberculosis is very rare among CF patients, and CD8 T cell activity may be a protective factor for CF patients against this disease. The role of the CD8 T cell response in the CF immunity as a whole also needs to be better investigated.

## What is next?

We still need to do a deeper investigation in a greater number of patients in order to have our hypothesis supported. For this, we aim to compare the response against *M. tuberculosis* and BCG with the response against NTM, to look for cross-reactions. We will also use other techniques to investigate which signalling components of the immune system create these responses in CF patients. Finally, we will compare the responses between CERFC patients and



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CF patients that are not BCG-vaccinated, so we can look to the influence of BCG vaccination in the frequency of NTM infection.

## **Original manuscript citation in Pubmed**

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