A new dual-action medication to cause double-trouble for Tuberculosis

Mycobacterium tuberculosis | drug resistance | antibiotics | subsequent delivery

Background

Tuberculosis is once again a threat to the world, especially due to the multi-drug resistant species that have infected around 500.000 humans world-wide in 2015 alone. Treatment options for these patients are limited and expensive, and more dramatically, in some cases completely absent; clinicians have no cure for these patients. Using high resolution microscopy techniques we discovered that upon antibiotic treatment the DNA of Mycobacterium tuberculosis condenses into a single clump (Figure 1). Recovery from this condensed state turns out to be a not yet discovered weak spot of the bacteria. By using this weak spot we could influence survival of the bacteria dramatically. This is a whole new approach in antibiotic treatment for these pathogenic mycobacteria. Since other bacteria condense their DNA in a similar fashion, the approach will likely also be applicable for other pathogens.

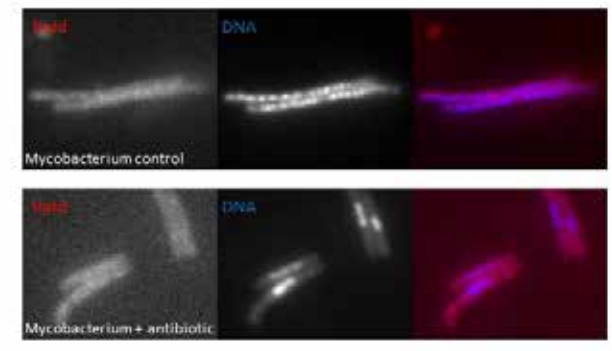

Figure 1 Mycobacteria treated with antibiotics relocate their DNA in a clump after antibiotics

Invention

The dramatic effect on M. tuberculosis survival is paralleled by the simplicity of the application. We want to develop an oral formulation that will initially release the antibiotic in order to condense the DNA of the bacteria, and subsequently release inhibitors for DNA binding proteins. Timing is important since we have demonstrated that the order of release is crucial. The subsequent release of multiple compounds from a single administration to induce DNA condensation is a novel strategy for antibiotics. We aim to utilize a combination of known compounds and methods, which makes this idea very cost-effective and fast to implement.

The capacity of mycobacteria to condense their DNA upon antibiotic stress has not yet been described in M. tuberculosis. Since we have shown we can manipulate this process, it can be targeted in a strategy to kill bacteria by disrupting the decondensation. The antibiotic and inhibitors are specifically affecting mycobacteria and could therefore be safely used in patients. We have demonstrated that this strategy works, even for multiple inhibitors.

In Vitro Data

The idea of subsequent delivery of antibiotics has been tested on bacterial cultures and discovered and analyzed with fluorescent and electron microscopy. In addition, we demonstrated that it is possible to manipulate the mechanism of condensation, or more specifically, the recovery after condensation. The survival of the bacteria was determined using the optical density of the cultures and the capacity to form colonies. All these outputs were reduced after the combination therapy.

We have tested the feasibility of this approach and demonstrated that the reduction of bacterial survival after the combination treatment is significant. The results of these studies are summarized in a manuscript soon to be published. Experiments in Zebra fish are ongoing and in the future follow up experiments in mice will be necessary.

Applications

The TB field is yearning for new approaches for antibiotic treatments as multidrug, extreme drug and even total drug resistant strains are a big threat to the health care system in Africa where up to 20 % of the TB-patients have drug resistant tuberculosis. These strains are currently also detected in Europe and are extremely difficult to treat. The costs of treating these drug resistant strains is immense (€ 94.000,- per patient versus € 324,- per susceptible patient). More importantly, the patients need to be cured.
As the approach is so novel and not yet applied in antibiotic / microbiology field, the application might extend to other bacteria as well. It is well known that drug resistance is an emerging problem throughout the whole microbiology field and new strategies are urgently needed.

Intellectual property

The production of the formulations with multiple antibiotics is already established and some different approaches, such as the extended release, were already shown to be effective. Therefore, technically the production of these formulations should be feasible. This knowledge can be combined with the newly discovered weak spot of mycobacteria described here. We would like to discuss possibilities to collaborate with companies that have been developing bi-layered antibiotic tablets after proper validation of the concept.
We are currently preparing a patent on this subject.

Inventor

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What are we looking for?

Licensing partner for this application as well as a collaboration partner for the evaluation of in vitro data and to extend the existing data set with in vivo data.

Key publication

Enzo M. Scutigliani, Edwin Scholl, Anita E. Grootemaat, Sadhana Khanal, Jakub A. Kochan, Przemek M. Krawczyk, Atefeh Garzan, Huy X. Ngo, Keith D. Green, Sylvie Garneau-Tsodikova, Jan M. Ruijter, Henk van Veen, Nicole N. van der Wel. Exploiting nucleoid-condensation to kill Mycobacterium tuberculosis. Submitted.