New approach in the fight against antibiotic resistance

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According to the WHO, around 700,000 people die every year as a result of antibiotic resistance. In Germany, around 6,000 people die every year because treatment with antibiotics is not effective. Scientists at Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU) and the University of Oxford have now discovered that there is a point in the production

process of the proteins at which it can be regulated by bacteria. This could be used as a starting point for the development of new antibiotics and help overcome resistance to antibiotics.

Antibiotics are used in the treatment of bacterial infections. They kill and inhibit the growth of bacteria, allowing the infection to subside and the patient to recover. However, during the last few years, increasing numbers of bacteria have developed so-called antibiotic resistance, which means they are resistant to the effects of antibiotics. Over time, these types of medication become ineffective and multi-resistant bacteria become even more widespread as a result.

Investigation of early phase of RNA synthesis

The discovery, which has now been published in the scientific journal *Nature Communications*, could be a completely new starting point in developing antibiotics. "New drugs could now be developed on the basis of our findings that kill the bacteria that cause illnesses," said Dr. David Dulin from the Interdisciplinary Centre for Clinical Research at FAU. The FAU team led by Dr. David Dulin and the team led by Achillefs Kapanidis at the University of Oxford have discovered that the early phase of ribonucleic acid (RNA) production is the key to controlling the regulation of bacterial gene expression. Gene expression is the term used to describe how a gene product coded by a gene is is formed . These products are often proteins, or RNA molecules.

In bacteria, the RNA is produced using a large protein complex called RNA polymerase (RNAP). The RNAP reads the DNA sequence and builds a copy of the RNA by joining nucleotides together—the fundamental building blocks of RNA—during a process called transcription. Since this production of RNA is fundamental for the survival of the bacteria, it has already been the subject of intensive research and used as the starting point for developing antibiotics, for

example for the treatment of tuberculosis. However, it remained unclear how the production of RNA is also regulated at the stage of early transcription when RNAP has just begun to join together the first few RNA building blocks. This was the subject of the research carried out by the team of scientists.

The researchers used high-end fluorescence microscopy, which allowed them to monitor individual RNAP molecules as they started to produce RNA. They discovered that the initial RNA synthesis is strongly regulated—a certain sequence of DNA forces the RNAP to pause for several seconds. It can only continue with RNA production after this pause.

This discovery completely changes our previous understanding of initial RNA synthesis in bacteria. "The fact that the RNAP can be simultaneously bound to the DNA and the short piece of RNA for a longer period of time was very surprising, as it contradicts current knowledge," says Dr. Dulin. The discovery of this new checkpoint in gene expression could be used for the development of new antibiotics. "For example, it may be possible to develop medication that locks the RNAP in the paused state, thus killing the bacteria that cause illnesses," says Dr. Dulin. The findings represent a glimmer of hope in the global struggle against antibiotic resistance.

More information: David Dulin et al, Pausing controls branching between productive and non-productive pathways during initial transcription in bacteria, *Nature Communications* (2018). DOI: 10.1038/s41467-018-03902-9

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