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Antibiotic resistance is one of the biggest upcoming challenges for the society. Bacterial populations typically consist of huge numbers of individuals and this means that when we use antibiotics there are always a few bacteria that, by chance, have the ability to resist the effects of the drug. This combined with their ability to reproduce at staggering speed (doubling as often as once every 20 minutes) means that such resistant bacteria can easily spread and multiply. As a result, over many years, the widespread use (and overuse) of antibiotics has lead to a rise in resistant bacteria. Unfortunately this rise has coincided with a lack of new antibacterials being developed, meaning that we are fast running out of effective treatments. Ultimately this could lead the frightening spectre of a return to the pre-antibacterial era where an infected cut or a cough could be a death sentence rather than a minor inconvenience. A recent example is the emergence of transmissible resistance to the antibiotic "of last resort" colistin in China.

The lack of new antibiotics being produced by pharmaceutical companies means that academic labs need to make bigger commitments to solving this problem. One important contribution is to further our understanding of how resistance works. Some of the most popular existing antibacterial drugs work by interacting with an enzyme in bacteria called “gyrase”. An enzyme is a tiny protein machine and gyrase`s job is to coil up DNA (a process known as supercoiling) something which is important in order for the bacteria to properly copy its DNA. Bacteria cannot survive without gyrase. As part of its job, gyrase passes a double-stranded DNA fragment through a break that it briefly makes in another part of the same DNA molecule. The famous fluoroquinolones drugs (FQs, e.g. ciprofloxacin), drugs targeting gyrase, cause it to release the broken DNA before it has had a chance to reseal it – this spells disaster for the cell. Unfortunately the clinical success of FQs is now threatened by the emergence of quinolone-resistant strains presenting a serious threat to society.

Interestingly, FQs were developed as fully synthetic compounds not existing in nature, which should have had limited the ability of bacteria to development of resistance. However, resistance ensued: some bacteria produce specific proteins (pentapeptide repeat proteins, PRPs), which are able to give such resistance. In normal “natural” circumstances bacteria use PRPs to protect gyrase from various toxins produced by their natural competitors in the environment. The bacteria have quickly adapted the PRPs to provide protection to gyrase from the effect of FQs. In this case the PRPs are termed “resistance factors”.

Some of these PRPs (like the Qnr proteins) are resistance factors transferred on plasmids, small pieces of DNA separate from the main chromosomal instruction set of the cell which can easily be transferred from bacteria to bacteria. The ease of transfer has led to these factors becoming widespread and contributing to the dangerous world we now live in where antibacterials are becoming ineffective.

Despite almost 10 years of study, the mechanism whereby PRPs protect gyrase from the effects of FQs remains elusive. Understanding it could help us to design ways to equip FQs with ways around the problem or even to design new types of antibacterials.

One of the features shared by all gyrase-affecting PRPs is DNA mimicry: the PRPs resemble the long thin shape of DNA as well as its pattern of electric charge. This has led to the idea that PRPs take the place of DNA inside the enzyme, stopping the DNA breaks being released by FQs. Whether this is true and how exactly it could be possible, is currently unknown. In our work, we aim to understand, at the level of the molecule, how protection against FQs by PRPs, works. This knowledge will enable the design of new drugs that avoid such resistance or even exploit it (because some PRPs actually achieve their effect by stopping gyrase from functioning, which makes the cell sick, they could, ironically be used as the basis of an antibacterial drug).

We will achieve this by using many different kinds of approaches including cutting-edge biophysics and biochemistry. These include methods that allow us to understand the structures of the participating molecules in high detail as well as how they interact with each other over short time scales as gyrase carries out its function. We will investigate previously underexplored PRPs that give a very specific high-level of protection to gyrase against natural products. By focusing on differences between these PRPs and the specific features that allow them to target gyrase, we will be able to produce a model of how PRPs work. We hope that such am model will prove useful in the continuing fight against bacterial resistance.