“Lords Of The Rings: How Bacterial Enzymes Convert Peptides Into Antibiotics”

The world has changed since antibiotics, such as penicillin, were introduced into general practice. Our initial victories against bacteria are now a distant memory. We now understand that the war with bacteria never can be permanently won, as they quickly become resistant to the deployed drugs. Indeed, the big part of modern medical technology – cancer treatments, surgeries, transplantations – all depends on the ability to control bacterial infections. Antibiotic-resistant pathogens are now expected to be a leading cause of death by 2050. Scientists are constantly looking for new antibiotics, but they are increasingly difficult to find. Perhaps, a better solution is to learn how antibiotics are made in nature, and then artificially design the new ones. Like the most of living matter, antibiotics consist of building blocks – amino acids – linked together into peptides. The bond joining amino acids together, is called the peptide bond and is very strong. For example, spider silk, entirely made of protein, is stronger than steel. Peptide bonds are inert – they don’t like to participate in chemical reactions. Humans have learned to synthesize simple peptides in test tubes, but we cannot easily introduce other chemical functionalities, for example rings or “heterocycles” in them. When bacteria make antibiotics, they use special enzymes to modify peptides in multiple ways, including introducing heterocycles, making chemists jealous. Luckily, bacterial enzymes are not very picky. If we can give artificial peptides to them, they are likely to modify those peptides as well, to produce novel antibiotics or medicines. Of course, there are some rules we need to follow. Enzymes are essentially tiny machines or nanomachines. Therefore if we bioengineers want to mimic mechanical engineers, who use blueprints to understand how the machines work, we need to have the “blueprints” of proteins to understand how they work.

How can we look inside something as small as proteins and take a “picture” to provide us the blueprints? There are two different ways of doing it. First one is “x-ray crystallography” – when crystals of protein are grown and then irradiated by x-rays. In a way this is similar to the medical x-ray scan, but uses a very powerful x-ray source – synchrotron radiation. Unfortunately, sometimes the crystals of protein are difficult to obtain. Then one can use another approach – flash-freeze proteins in very thin ice to preserve them intact, and image by a powerful electron microscope. This is called “cryo electron microscopy” – a technique for which a Nobel prize was given in 2017.

Both of these methods are now accessible in Cracow at Solaris national facility. We will use them to study molecular machines making two peptide antibiotics – klebsazolicin and microcin B17. When the structures of antibiotic-making enzymes are known, scientists can engineer them to accept very different peptides and modify peptide bonds according to our needs. The future antibiotics could be then predicted in a computer and produced biotechnologically or semi-synthetically to make sure we have enough potential drugs in the pipeline.