NOVEL ANTIBIOTIC DESIGN: IN SEARCH OF A MAGIC BULLET

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THE BUG–TUBERCULOSIS

Tuberculosis (TB) is a disease caused by an infection, most commonly in the human lung, by the bacterium *Mycobacterium tuberculosis*.

The disease is rife in many developing countries, but is also a problem in New Zealand. Annually, about 2 million people die from TB, and in the period 1999 to 2001, there were 1,172 notified cases in New Zealand.

The emergence of antibiotic resistant bacteria is of great concern because such infections can no longer be treated with standard antibiotics and are lethal.

Marry antibiotic resistance with a devastating disease, such as tuberculosis, and we have a problem.

To overcome the emergence of antibiotic resistance, our goal is to develop a new antibiotic with a novel mode of action.

THE STRATEGY

Traditional antibiotics work by inhibiting the function of essential enzymes (protein catalysts) in the bacteria **(Figure 1)**. If the enzyme can't work, then the bacteria can't divide.

Enzyme targets are carefully selected to avoid enzymes important to human cell survival. We have been investigating a bacterial enzyme called dihydrodipicolinate synthase (DHDPS). This enzyme is essential for bacterial survival, but is not found in humans, so inhibiting it will be safe.

Like many enzymes, DHDPS requires a number of protein units to bind to make the functional enzyme. For DHDPS, four identical protein units join to make the functional structure.

Any molecule that inhibits the formation of an enzyme's quaternary structure will inhibit the enzyme* (Figure 2), *and therefore, bacterial growth.

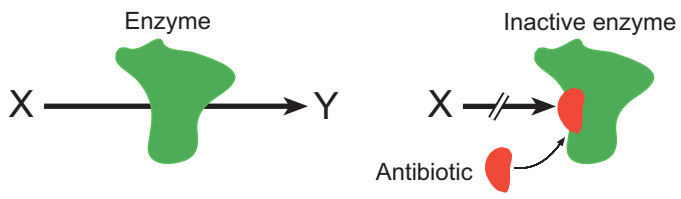

Figure 1. Traditional antibiotics (such as penicillin) at work. The antibiotic (red) binds to the active site of the enzyme (green) and prevents it from transforming X to Y. Without Y, the cell cannot grow and divide.

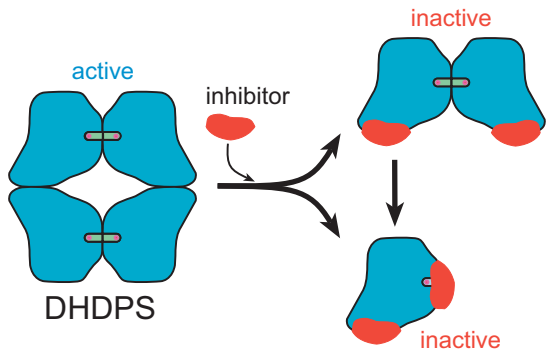

Figure 2. Breaking up the structure of DHDPS. When the four protein units are split (to either one or two units), the enzyme can no longer function. The number of protein units is known as quaternary structure.

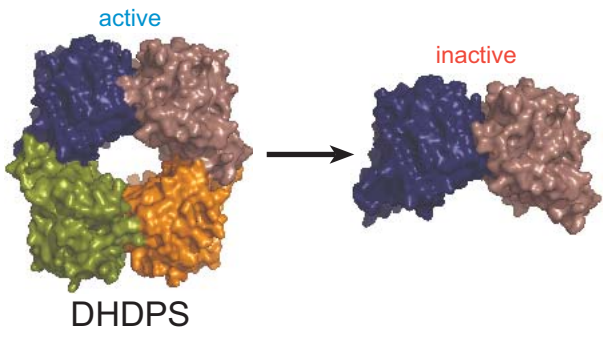

Figure 3. The dimer of *E. coli* is inactive.

THE RESULTS

We tested our ideas using *Escherichia coli* as a model system. This infectious bacterium causes gastroenteritis and like *M. tuberculosis*, has a very similar (and essential) DHDPS enzyme

We changed the structure of DHDPS from *E. coli* to show that the complete structure (all 4 protein units) is necessary for function **(Figure 3)**.

Using a model of the enzyme's structure, a molecule (*ITP-3* §) was designed to bind tightly to the surface of the *E. coli* DHDPS, block the normal protein units from forming, and therefore stop the enzyme from working.

ITP-3 changed the enzyme's structure, inactivating its vital role in the cell.

Not only does the inhibitor affect DHDPS function, it also inhibits* E. coli *growth!!

THE FUTURE

Having shown the principle works for *E. coli*, work is underway to design similar molecules that will inhibit *M. tuberculosis* DHDPS and ultimately TB infections.

Inhibitors can be designed that are specific for only one bacterial species, because different bacteria have slightly different DHDPS structures. This means "good" bacteria, such as those in the gut, will not be affected.

Collaborators: Mike Griffin, Matthew Perugini (University of Melbourne), Geoffrey Jameson (Massey University), Juliet Gerrard, and Genevieve Evans (University of Canterbury).

§ ITP-3 is the subject of a patent application so its identity cannot be revealed; we have formed a partnership with Industrial Research Limited in order to move the lead compound and its derivatives closer to the commercial arena.

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Poster design by Matt Walters