By Kirsten Rodenhizer

Twenty years ago Dr. Edward Ishiguro came up with a solution to a problem that had stumped scientists since the discovery of penicillin in 1928.

That problem was penicillin tolerance — penicillin's inability to kill bacteria when they are not growing. Growing bacterial cells are susceptible to penicillin, but non-growing cells are tolerant.

Though scientists had long been aware of this phenomenon, they had not been able to overcome it. Not, that is, until Ishiguro, who is now chair of biochemistry and microbiology at the University of Victoria, realized tolerance was directly related to cell starvation.

Ishiguro had long suspected a connection between cell starvation and penicillin tolerance, and he still remembers the moment that he realized how he could test his theory.

"It was a rainy Saturday afternoon idea that just cropped up," he says. It turned out to be the idea that launched his career.

Penicillin and similar antibiotics work by targeting the cell wall of bacteria. Starving or non-growing cells produce a chemical called guanosine tetraphosphate which acts a signal for the cell to shut down its energy-consuming operations and go into stasis — a state of inactivity.

"It's like an energy conservationist turning off all the lights when no one is at home," says Ishiguro. "Happy cells don't create this chemical."

Using E. coli bacteria as a model, Ishiguro developed a test that showed that guanosine tetraphosphate triggers a shutdown response in penicillin's target — a protein responsible for the construction and expansion of the cell wall — making it impossible for penicillin to interact with it and destroy the bacteria.

Subsequently, Ishiguro found that he could inhibit the production of guanosine tetraphosphate in starving cells.

"Guanosine tetraphosphate — the starvation signal chemical — is made by a protein associated with the cell ribosome, the structure on which cell proteins are produced," says Ishiguro. "We found that drugs that target ribosomes, by pure chance, inhibit the formation of the chemical." This fools the bacteria into behaving like normal growing cells and keeps them susceptible to penicillin.

Ishiguro says that while a combination of these ribosome-targetting drugs and penicillin can kill non-growing bacteria, such combination therapy isn't perfect.

"They don't target the specific action of the protein, and, moreover, many bacteria have already become resistant to these drugs." Resistance — which is not the same as tolerance — results when bacteria adapt to an antibiotic that has been in use for a long time.

For the past two years, Ishiguro's team has been studying the protein that releases guanosine tetraphosphate, an effort that could lead to drugs that block its specific action. This protein may represent an important new drug target.

"The discovery of new drug targets is so important today due to the growing problem of bacterial drug resistance," he says.

Research into guanosine tetraphosphate is also crucial because scientists have found the chemical allows bacteria to resist the body's defence mechanisms as well as drug treatment. Starving cells, for example, can tolerate acid attacks in the stomach.

"The human body has perfectly good defence mechanisms,"says Ishiguro. "If we can short-circuit the production of this chemical we can make bacteria more sensitive to both drugs and the body's own defences."

Ishiguro has received funding from the Natural Sciences and Engineering Research Council for 20 years. He now receives more than $60,000 a year from the agency.

"Without that funding I would not have come very far," he says. "It has supported many of my students, who are all doing very well now."

Teaching and research, a symbiotic relationship

Like all UVic faculty members, Dr. Ed Ishiguro is both a teacher and a researcher. For him, the two go hand-in-hand.

One part human, ten parts germs

The adult human body is composed of about 10 trillion human cells. In addition, it is home to approximately 100 trillion microorganisms (a.k.a. "germs").

The microbes that live on humans are called the normal microflora, most of which are bacteria in the intestinal tract. Far from threatening our health, the normal microflora play an essential role in keeping us healthy. They apparently provide a competitive barrier, preventing harmful microbes from invading our bodies. Although some of our normal microflora could cause serious diseases, in healthy people their activities are kept in check by other members of the normal microflora.

Our resident microorganisms are important, and we should care for these microbes as much as we care for our own cells (for example, eating yogurt to help re-establish your intestinal microflora after being treated with a course of antibiotics).

Keeping one step ahead of the microbes

Antibiotics are chemicals produced by living things that prevent the growth of microorganisms and, in some cases, even kill them.

Only a small fraction of the known antibiotics are used to treat human disease. Many antibiotics have toxic side-effects that are harmful to humans.

And the number of these useful antibiotics continues to decrease at a frightening pace. Microorganisms rapidly develop resistance to antibiotics and, once that happens, they are no longer affected by them. The more we use antibiotics, the more microorganisms build up resistance to them.

Developing new antibiotics that are effective against these resistant microbes is a major priority. The problem is that we are quickly running out of options. Therefore, to prevent the spread of antibiotic resistance, we should use antibiotics only when it is absolutely necessary.

Art 2000 International Exhibition
Through May 31
Artwork from Australia, China, Canada and Northern Ireland by students from their kindergarten year of 1988 to their graduation in the class of 2000. Maltwood Art Museum & Gallery, University Centre. Info: 721-6562

Workshop: "Seafood Sustainability in a Changing Climate"
May 25-26
Fishing industry leaders, climate researchers, policy makers, and coastal community representatives will explore ways to mitigate climate-related threats to B.C. fisheries. Agenda details and registration info: www.cics.uvic.ca/workshop

Operation Trackshoes
June 10-11
A sports festival for the citizens of B.C. with a mental disability. Opening ceremony, June 10, 8:30 p.m. Centennial Stadium. Competition, 9 a.m. to noon, Centennial Stadium. Wheelchair games, June 11, 9 to 11:30 a.m., McKinnon Gym. Closing ceremonies, noon, Centennial Stadium. Info: 721-2233, www.trackshoes.bc.ca

24-Hour Relay for the Kids,
June 24
Sponsored by the Lions Society of B.C. for children with disabilities. Proceeds go to sending children with disabilities to Camp Shawnigan. Relay begins at 10 a.m. Centennial Stadium. Info: 386-0668