Black Belt In Research

University of Calgary biological sciences professor Dr. Andre Buret pits himself against the microorganisms that wreak havoc in the guts and lungs. Find out who's winning.

When Dr. Andre Buret first moved to Canada, it wasn't enough for him to simply settle into a new country and focus solely on the challenges that it entails. He also decided he wanted to pick up another extra-curricular activity: karate. Along with its physical aspect, karate bestows on its devotees a mental focus – something that Buret says definitely helps him in his work as one of Alberta's most innovative biological research scientists.

"I started it then and have been with it for 18 years," confirms Buret, a professor at the University of Calgary, about karate. "I had done a lot of sports before in Switzerland, and martial arts is one thing I knew nothing about. I was curious about it."

"I have now reached the rank of instructor (shidoin, third degree) and help teach with a club here," he adds. "And that's a good thing, because, besides its physical component, karate has a very important psychological aspect to it that's very useful to me and my profession, and in life."

If it does have that kind of impact, perhaps the people and livestock that Buret helps through his research should also be thankful for the benefits of karate. Because as an Associate Professor in both the Department of Biological Sciences, Faculty of Science, and the Mucosal Inflammation Research Group (MIRG), Department of Pharmacology and Therapeutics, Faculty of Medicine, Buret is able to effect real change. His principal interest is in the study of infections – primarily in the intestine, lungs, and eyes. He is devoted to finding out how these organs respond to disease.

Once that is determined, Buret searches for ways to "actually bend the development of clinical symptoms," as well as develop therapies. Diseases are often the direct result of infiltration by microbes, but Buret would like to determine whether a host's own immune responses can also be a trigger for disease, regardless of the involvement of any microbes.

The disease that currently commands the bulk of Buret's attention? Gastrointestinal disease, which, amazingly, is responsible for the death of more than five million of the world's children under the age of five every year.

One of Buret's most significant accomplishments to date is his contribution to the development of a "silver bullet", as he puts it, to combat such intestinal abnormalities. Derived from a protein found in milk, Buret and his collaborators are now working to get this potentially gut-altering, life-affirming product to market. They are attempting to do so through a company they spun off from the University of Calgary for the purpose of commercializing the drug.

"One of my other jobs is to help run that company," acknowledges Buret of AB BioPharma Inc., where he sits on the Board of Directors. "We're at a stage where we already have a successful pilot clinical trial. I hope that in the next five years we would be able to launch our first product."

Ross Bricker, Vice-President, Investment with AVAC Ltd., a value-added agriculture investment company, shares Buret's optimism. In fact, AVAC as a whole is so pleased with the professor's fight against gastrointestinal disorders it has financed the battle to the tune of $1.25 million in total investment in AB BioPharma Inc. – making AVAC the company's biggest investor.

"(The investment) speaks to our level of interest in the opportunity, and our expectations for its success," says Bricker. "What's so interesting to us about the project is the presence of a world-class group of researchers who have identified a product that has significant benefits to both human and animal health, both for prevention and treatment; a market demand that's substantial; and a management team that's solid. They're moving forward quite quickly in terms of attracting the additional investment required to successfully launch the product in the market. So it's a good project all the way around."

It's simply a bonus that the man leading the project is as sunny as he is, adds Bricker. "He's an upbeat individual and he tends to bring up the level of interest in people around him. You enjoy being around him," he says of Buret.

Malabsorption Syndrome

Buret began his work in this area by first concentrating on malabsorption syndrome. When the body is absorbing liquids properly, there is a membrane that plunges finger-shaped microvilli – little hair-like structures – into the intestinal tube, thereby increasing the absorption area of the intestine. Buret, however, noticed that when affected by microbial infections or disorders such as Crohn's disease, food allergies, and celiac disease, the epithelial cells of the small intestine undergo significant changes.

"What we have found is that in a number of diseases you have an enormous loss, or shortening, of these microvilli. They just get shorter and stubbier," says Buret. "As if the cell would pull these fingers back in and say, 'oh, there is nasty material out there, let's not expose ourselves too much to that.' But as they do that, they also, of course, can absorb much less, and you have malabsorption."

Through observation, Drs. Grant Gall and Jim Hardin, two of Buret's current collaborators on this technology, eventually realized that there is a product that

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actually manages to reverse this process. Not only that, but as his team did more studies, they also discovered that if this product was given to an experimental animal that was subsequently infected with E. coli bacterium, the E. coli could not stick to the intestine. To quote an info sheet that describes Buret's work: "If the bacteria don't stick, then they won't make you sick."

"Basically, the product protects the intestinal surface from infection," says Buret. "So not only have we shown that it works on an ongoing infection, but we have since shown that it works if you give it before the establishment of infection. It works in the stomach, it works on viruses, bacteria, and parasites, and it works in a number of animal species."

At present, Buret and his team have established 16 patents worldwide on the usage of this product. Along with the establishment of, and investment in, its marketing company, Buret has other reasons to be excited about this product.

"It's not an antibiotic, not a hormone, and because of that, all of a sudden, it has tickled a lot of interest," says Buret. "There is a lot of discussion in the agricultural industry about the use of antibiotics, and crossover of antibiotic resistance to humans, and so forth. Perhaps if someone could use this as an approach, you could replace antibiotic usage in the agricultural industry."

In humans, the possibility exists that this could be the answer to many common gastrointestinal disorders, such as diarrhea. Once completely manifested, Bricker sees the technology as being able to be used on "a day-to-day basis", with tourists, for example, having the option to "pop a pill" in any country where they might otherwise be exposed to gastrointestinal problems.

In livestock, both the product's preventative and therapeutic benefits are highlighted once again. "There are a number of diseases in domestic livestock that involve gut problems," says Bricker. "The way this product works is it affects the permeability of the gut to invasion by bacteria and viruses. Any time these animals are being moved, or being weaned, they're at risk for bacterial or viral infections."

"This is a product that can help to improve the resistance of the individual animal to infection and, secondly, can also be used as a supporting therapy for treatment of those animals if and when they become ill. So it affects both sides," Bricker says.

Given the potential wide-sweeping markets this product may have, Buret is considering all options, including the product's final physical form. "It will be delivered orally, so you will have to eat it. In this way, it can take any shape or form. Whether it's (for) a puppy dog, or your grandmother, the shape is going to change," laughs Buret.

Inflammation

A force in the study of gastrointestinal disease, Buret is also a black belt when it comes to combating pulmonary diseases (those which affect the lungs) – particularly in his dedication to better understanding inflammation, which is the body's own response to coping with foreign invaders. However, inflammation can become an "exaggerated and deregulated" host response, making it detrimental. Buret set about to determine the extent to which inflammation might be reduced through reinforcement of apoptosis in neutrophils – apoptosis, also known as "programmed cell death", and neutrophils referring to those immune cells that the body releases in response to bacterial infection.

"One of the things that has come out recently is (the observation that in) infectious diseases, like pneumonia, what really kills the host is not the bacteria that infect the lungs, but your immune cells

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that accumulate in the lung in response," says Buret.

"One of the mechanisms whereby these neutrophils attack and kill bacteria is through the release of a number of toxic compounds, including acids similar to commercial bleach. In that process, not only are the bacteria going to be in contact with this material, but also your own pulmonary linings. Ultimately, that exaggerated inflammation eventually destroys the lung, pulmonary failure ensues, and then, ultimately, death."

Working backwards from this point – in an effort to answer the question "can this process be curbed?" – Buret hypothesized that perhaps there are already products in existence that work to limit inflammation, but it's just that no one has realized it yet.

His hypothesis was right. He found just such a product in the drug tilmicosin, which is manufactured by Elanco, a division of Eli Lilly. The advantage was finding a product to study that was also "clinically significant and relevant for society."

Tilmicosin is used to treat shipping fever, a condition that occurs in cattle during periods of high stress – like the move from farm to feedlot. In healthy cows there is a bacterium that usually resides in the upper respiratory tract. When the animals are under duress, these microbes can spread more than they should, and infiltrate the lower respiratory tract. After that happens, death can occur within 48 hours.

However, one single injection of tilmicosin to an infected animal and it walks away, says Buret. "The reason why it works – and that's the mechanism we have discovered – is because this antibiotic has the capability of telling these inflammatory cells, the neutrophils, that as soon as they are in contact with the drug, they are to be switched on to die by suicide, instead of exploding on site (otherwise known as necrosis)," says Buret.

"They still do their job – they use their two to three-day life span to go to the lung, kill the microbes, and migrate the way they should – but then instead of exploding on site and releasing all that acid and other noxious compounds, they implode. They keep their membranes around themselves and are cleaned up by surrounding cells, which ingest them, and destroy them internally. In that fashion, you curb inflammation."

Buret suggests that this process of "reprogramming" cell death could become a new mode of action for other antibiotics. The rationale is that not only will antibiotics be beneficial when they kill bacteria, but with diseases like these, they may even be better if they can curb inflammation via this mechanism.

"Obviously, the company (Elanco) is interested for other reasons. (This research) will have marketing benefits, absolutely," says Buret, who says Elanco has become a major investor in his pulmonary work for this reason. "This said, it is a very new theory, and as such, it is very controversial. But there are some groups, including one in Germany, who have become very interested in this, and have since reproduced the observation. So it's slowly getting out there."

Coming From a Different Angle

Buret discovered the hidden benefits of tilmicosin by coming at a situation from a different angle. He applies the same technique to his teaching, and encourages the same kind of thinking in his students.

Nowhere is his innovation more evident in the classroom than in his launching of the Principles of Parasitology course at both the University of Calgary and the University of Alberta in 1996. That's right – through the magic of video-conferencing, Buret and his counterparts in Edmonton, either Dr. Mike Belosevic or Dr. Al Shostak, can teach two classes of undergrads at the same time.

"The course may be directed, or principally lectured, from one site. But the other prof at the other site intervenes," describes Buret. We really try to put a lot of humour into it."

The formula works, as evidenced by Buret being the first non-University of Alberta professor to receive its Unit Teaching Award, which he won in 2001 along with Belosevic and Shostak. This year, Buret was also honoured at his home university, receiving the University of Calgary's Graduate Students' Association Teaching Excellence Award for 2003. The recent teaching awards are a fitting "closing of the circle" to a career that began, and will likely end, in education.

"In Switzerland, before completing a biology degree, I did, in fact, complete a teaching diploma at the elementary school level and taught at that level for five years," says Buret, his deep voice highlighted by a French accent that has never fully disappeared. "As time went by, basically, the target audience changed. I've been lucky enough to teach kids from Grade one all the way to post-doctoral fellows, and that's very rewarding."

It would seem that for this researcher and teacher, a black belt is a level of achievement that applies to more than karate. **r&d**