

## New treatment pending for CF

*Researcher defends cystic fibrosis sufferers from aggressive lung bacteria*

LIFE EXPECTANCY FOR CANADIANS WITH CYSTIC FIBROSIS (CF), A FATAL GENETIC disorder that leaves its sufferers highly susceptible to lung and digestive tract problems, stands at about 35 years. That's a significant improvement from 1960, when the disorder claimed most of its victims by the age of four. But it's still too brief, says University of Guelph microbiology professor Joseph Lam. After a decade of painstaking research, he's close to a discovery that may lead to the development of new treatment for CF-related bacterial infection, which can be fatal to Canada's 3,330 CF sufferers, half of which are children.

Lam has been working with genes and proteins to find a weakness in the pathogen responsible for a particularly dangerous lung infection. Specifically, he's been targeting the vulnerable outer coating of the bacterium *Pseudomonas aeruginosa* and is testing new antibiotics tailored to fight the culprit.

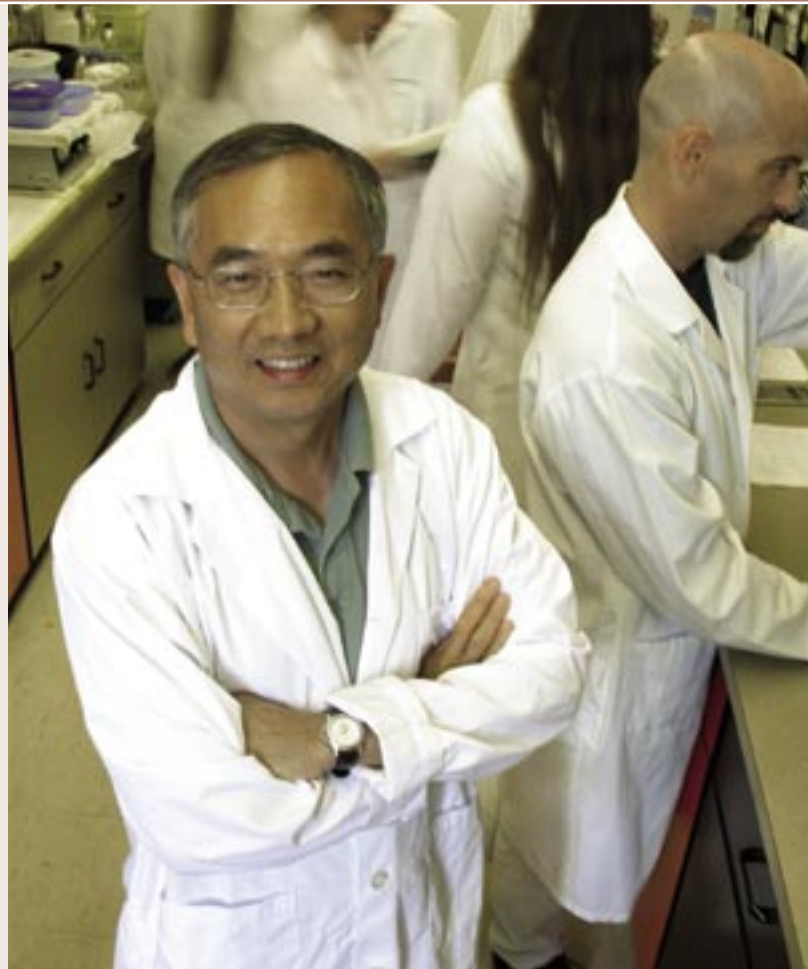
"Contracting a bacterial lung infection is similar to having the flu, but for CF patients, the flu continues," he says. "That causes great discomfort and irreversible damage to the lung due to prolonged pneumonia-like symptoms. We hope that by finding better antibiotics tailored against the lung infection caused by these bacteria, CF sufferers will lead even longer and healthier lives."

When a bacterium enters the lungs, it has ways to protect itself from the body's aggressive immune system. *P. aeruginosa*, for example, forms what is called a "biofilm" and coats itself with a complicated network of sugars called lipopolysaccharides (LPS). This protects the bacteria and allows them to adhere to the lung's surface, establishing infection.

Lam has devoted more than 10 years to gaining a better understanding of how the LPS coat is formed. He has identified the genes that control the protective coat and investigated each protein encoded by these genes individually, using complex laboratory equipment and cutting-edge techniques to purify and determine their function.

"It's important that we develop new drugs to fight *P. aeruginosa*," says Lam. "Replacing older antibiotics the bacterium can resist will give doctors better tools to help CF patients."

For Lam's work on CF, the Canadian Cystic Fibrosis Foundation named him the 2001 Marsha Morton Scholar, the most prestigious title



Prof. Joe Lam is destroying the protective coating on a bacterium that causes fatal lung infections in patients with cystic fibrosis.

bestowed by the foundation, and the 2002 Zellers Senior Scientist. More recently, he was awarded a Canada Research Chair in Cystic Fibrosis and Microbial Glycobiology.

Other members of Lam's research team include post-doctoral researchers Karen Poon, Priyanka Abeyrathne and Sonish Azam; graduate students Mauricia Matewish, Wayne Miller, Erin Mulrooney and Terence To; research assistants Cory Wenzel, Hamed Ghanei and Erin Anderson; and undergraduate research students Erin Westman, Jessica Cock and Ronak Shah. Also involved are collaborators Jean-Robert Brisson and Jinjuan Lee of the National Research Council, Carole Creuzenet of the University of Western Ontario and Albert Berghuis of McGill University.

This research is sponsored by the Canadian Institutes of Health Research, the Canadian Bacterial Diseases Network, the Canadian Cystic Fibrosis Foundation and the Natural Sciences and Engineering Research Council.

**Replacing older antibiotics will give doctors better tools to help CF patients.**

# Waging war on the waistline

*Guelph researchers examine obesity and diabetes, “the diseases of affluence”*

STUDY AFTER STUDY, HEADLINE AFTER HEADLINE, THE North American public hears the same thing: we eat too much and exercise too little. We’re too fat, and a consequence of our bulging waistlines is an increased incidence of type-2 diabetes (or adult onset diabetes). It affects more than two million Canadians and costs \$9 billion (USD) in healthcare and treatment each year.

“We eat too much for the activity level we maintain,” says University of Guelph Prof. Lawrence Spriet, Department of Human Biology and Nutritional Sciences. “We’re far less active today than in the past. There’s too much ease in our society and too much fat in our diets.”

Spriet and post-doctoral fellow Rebecca Tunstall are examining how fat breakdown in muscle is affected by both hormones and exercise in people who are either lean, obese or type-2 diabetic. They want to know how people burn fat

in response to exercise and adrenaline, and learn more about why obese and type-2 diabetic people have so much trouble breaking down fat.

In obesity and type-2 diabetes — what Spriet calls “the diseases of affluence” — patients become resistant to insulin, the hormone that signals cells to take up glucose from blood, causing blood sugar levels to rise. That can lead to excessive thirst, hunger, frequent urination and fatigue — and symptoms often get worse over time.

Here’s the problem: Muscle normally burns fat or carbohydrates for energy, depending on what’s available and the body’s energy needs. But type-2 diabetics lose that flexibility and can’t burn fat normally. Fat is also involved in other signalling pathways in the body, so excess amounts can disrupt glucose uptake even further.

But Spriet and Tunstall are working to change this fate. In particular, they want to see how a crucial fat-burning enzyme — called hormone sensitive lipase — is affected by both adrenaline and acute exercise. Normally, adrenaline and acute exercise activate this enzyme and causes it to break down fat. But Spriet and Tunstall suspect that obese and type-2 diabetic individuals are less sensitive to these effects.

Spriet believes exercise training may restore adrenaline’s normal enzyme activation and enable these individuals to break down fat. Regular exercise — with its ability to increase the amount of fat being burned by muscle — fends off the effects of overeating and inactivity.

“The body adapts to the stresses it’s under,” he says. “Challenging the body with exercise promotes health. It’s an important way to maintain one’s ability to break down fat.”

Spriet and Tunstall are putting test subjects on an eight-week cycling program and testing how well the fat enzyme works before and after the regular exercise regimen. They are also testing volunteers for glucose handling, to see whether they’re insulin-resistant (a risk factor for developing type-2 diabetes). The researchers will also test body composition for body fat and fat-free mass to see how fat affects glucose uptake. They also want to determine participant’s oxygen uptake during the exercise sessions to gauge how their ability to burn fat is affected.

This information will give the researchers details about fat metabolism in muscle. They hope to observe a marked improvement in participants’ ability to burn fat after exercise.

“This study is about real people, doing real exercise in the real world,” says Spriet. “We’re studying the human body as a whole, so the results will have direct importance.”

Spriet and Tunstall are collaborating with Prof. George Heigenhauser, Department of Medicine, McMaster University. This research is sponsored by the Canadian Institutes of Health Research.

For more information, or to participate in the study, contact Dr. Rebecca Tunstall at (519) 824-4120 ext. 53651 or e-mail [rtunstall@uoguelph.ca](mailto:rtunstall@uoguelph.ca).



With the help of test subject Rob Moreland (right), Dr. Rebecca Tunstall and Prof. Lawrence Spriet are looking at how hormones and exercise can help people who are obese or type-2 diabetic.

# A wake-up call for coffee drinkers

*Study suggests caffeine consumption could impair metabolism*

THE WELCOME BUZZ FROM A MORNING CUP OF COFFEE can increase alertness and reaction time. But research at the University of Guelph shows it also impairs the body's ability to manage glucose in the long term. This could spell danger for pregnant women, type-2 diabetics and obese or sedentary individuals.

Prof. Terry Graham and Lindsay Robinson, Department of Human Biology and Nutritional Sciences and former graduate students Lesley Moiseley and Sita Kacker have been studying the "real-life" effects of caffeine on the metabolism. Their findings suggest that caffeine actually slows metabolism, something that may take coffee drinkers by surprise.

"We have the naïve impression that nutrition is simple — there are fats, there are carbohydrates and the rules are the same for everyone," says Graham. "But this study has shown that the reality is very different."

Graham's team studied the effects of caffeine following a typical breakfast of coffee and cereal. For the study, 10 healthy male participants aged 20 to 27 were given either caffeinated coffee, decaffeinated coffee or water, along with a serving of cereal and milk. Following breakfast, all of the participant's blood glucose (sugar) levels rose as they digested the meal. Their bodies naturally responded to the excess glucose by releasing insulin, to prevent glucose levels from rising too high, says Graham, which is a normal response.

But the caffeinated coffee drinkers released much more insulin than other participants. In theory, the large amount of insulin released in the body should have caused the glucose levels to drop quickly. But, three hours later, the glucose levels of the coffee drinkers had still not returned to normal. This suggests that caffeine reduces insulin's effectiveness — a condition known as insulin resistance.

Participants consumed a second meal three hours after breakfast, but this time without coffee. The insulin and glucose levels of the coffee drinkers spiked after the second meal, surpassing the levels of the decaf and water drinkers. Their glucose levels were still far above average five hours after the morning coffee, suggesting that the caffeine continued to cause insulin resistance long after it was consumed.

Graham says the body can take up to 24 hours to eliminate caffeine, which means an 11 a.m. coffee break could affect the body's ability to digest an evening snack. This doesn't

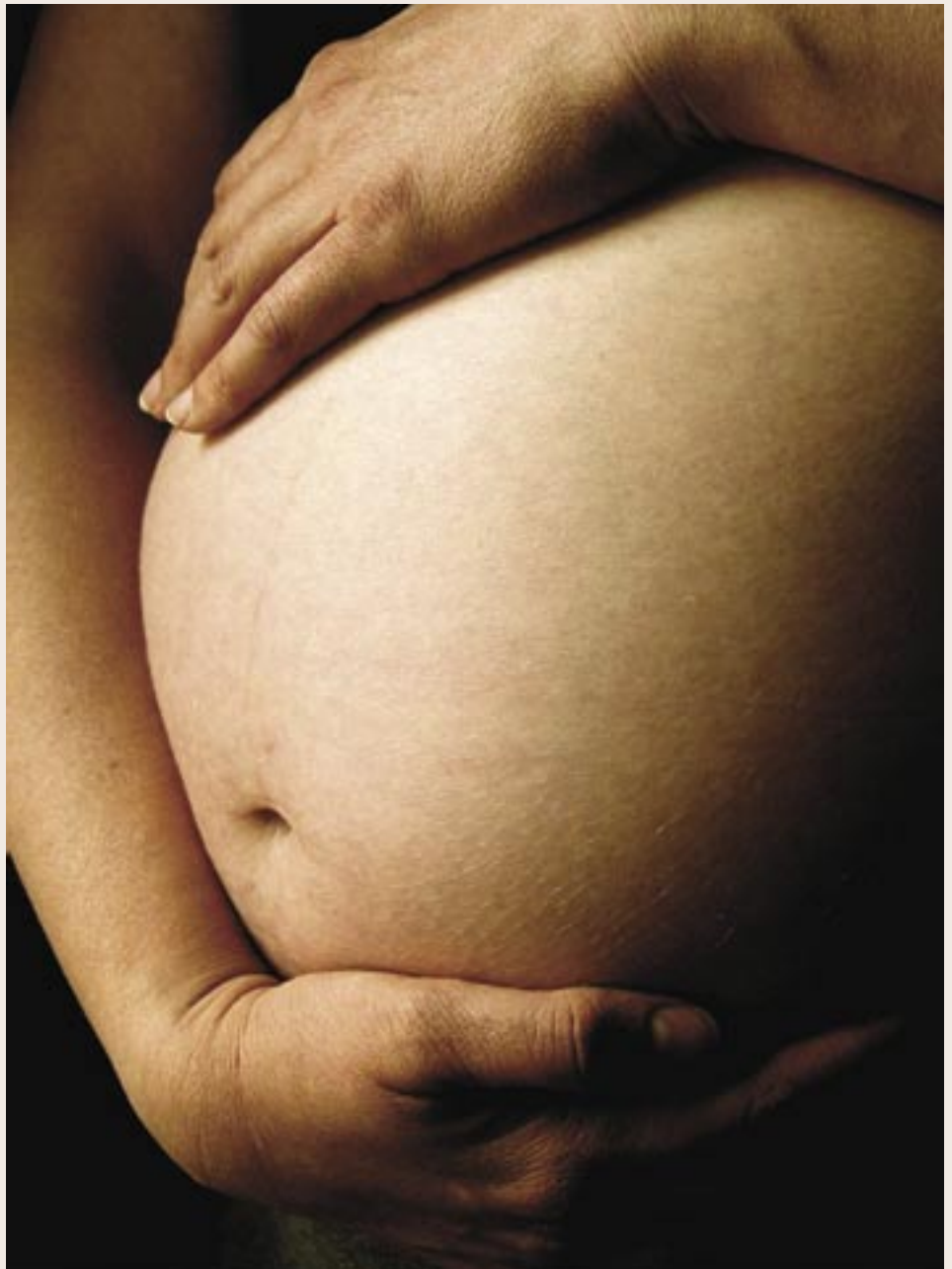
pose a significant problem for most people, but complications could emerge for people who are already struggling to manage glucose, such as type-2 diabetics and gestational diabetics (women who contract diabetes during pregnancy). Presently, Robinson and the research team have a paper in press in *The Journal of Nutrition*, showing that type-2 diabetics are more insulin-resistant when caffeine ingestion precedes carbohydrate consumption.

Diabetics don't have extra insulin reserves. When diabetic people use caffeine, their bodies

can't increase insulin production to manage glucose levels. This can cause blood glucose levels to soar dangerously high, suggesting that diabetics or those at-risk for diabetes might be better off to limit caffeine, Graham says.

This research is sponsored by the Natural Sciences and Engineering Research Council.

Pregnant women affected by gestational diabetes are among those at-risk groups who experience soaring insulin levels when they ingest caffeine.



# The power of prevention

*Understanding muscle metabolism is key to preventing obesity and type-2 diabetes*

METABOLIC DISEASES — SUCH AS OBESITY AND TYPE-2 diabetes — are on the rise, with an estimated 1.5 million Canadians now suffering from type-2 diabetes. Genetic susceptibility is a significant contributing factor, but environmental influences such as diet and exercise also play a key role.

Disturbances in sugar and fat metabolism in muscle tissue are closely linked to the development of these diseases. As the Canada Research Chair in Metabolism and Health at the University of Guelph, Arend Bonen is examining how the processes through which sugars and

fats entering muscle cells are controlled, at the molecular and biochemical levels.

Bonen's research focuses on the expression and function of transport proteins — efficient carriers of substances such as glucose (sugar) and fats across plasma membranes — that act as gatekeepers into the muscle cell.

By regulating entry into the cell, these proteins are involved in regulating the metabolism of sugars and fats.

Understanding how transport proteins are regulated may have important health outcomes, and help define how muscle activity and dietary nutrients may be used as low-cost, non-pharmacological interventions to prevent, or even reverse, selected metabolic diseases.

This research could also lead to a better understanding of how environmental influences, such as nutrition and muscle activity, alter the development of metabolic diseases.

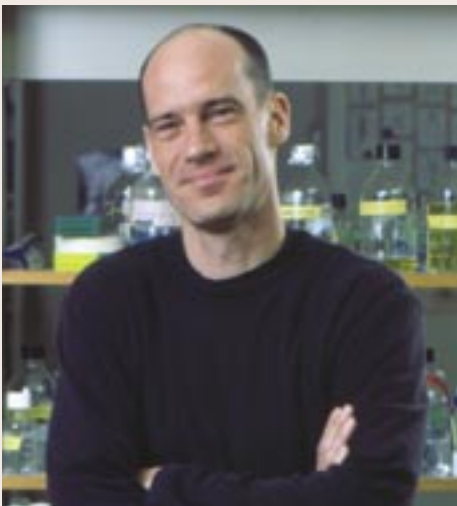
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Prof. Arend Bonen is studying the link between sugar and fat metabolism in muscle cells and metabolic disease.



# The chosen genes

*The way cells select specific genes could impact treatment and diagnosis of disease*



THE RECENT CHARACTERIZATION OF THE HUMAN genome and our growing ability to manipulate individual genes has allowed us to better understand the roles of genes in health and disease. One key component of this lies in the process of “gene expression” – the genes which a cell “chooses to use” at any given time and the way it makes such choices.

At the University of Guelph, Prof. Jonathan LaMarre, Canada Research Chair in Comparative Biomedical Sciences, is directing

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Understanding gene expression could lead to more efficient diagnosis of diseases such as cancer, says Prof. Jonathan LaMarre.

studies aimed at understanding how the expression of genes is controlled under different conditions and in different cells. LaMarre believes a better knowledge of gene expression could help in the diagnosis and treatment of diseases such as cancer and atherosclerosis.

In LaMarre's laboratory, gene expression is compared between different species and between healthy and abnormal cells in attempt to find important control mechanisms. Currently his research focuses on animal cells, with potential future applications in humans. Ultimately, his group hopes to develop a more complete understanding of how genes interact, the impact of their environment and the factors that control gene expression.

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