

THE LASER

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Giving Patients More Time: A Promising Treatment for Type 1

Patients recently diagnosed with type 1 diabetes often have some residual ability to make insulin. This capacity, however, typically reduces to zero over time. But a new experimental drug has been devised to extend the grace period, perhaps forever. PNRI principal investigator Dr. Bill Hagopian and his colleagues are beginning to test the drug's effectiveness. If it works as

insulin it requires. Only when the number of remaining cells grows dangerously small, do the symptoms of diabetes usually manifest themselves. Even then, when symptoms do appear, there are still some insulin-producing cells left. For a short while, therefore, a newly diagnosed patient retains some of his or her own beta cell function. This phenomenon has come to be called "the honeymoon period."

Scientists are uncertain about how many beta cells typically remain at the time of diagnosis or how many of these are still functioning effectively in the honeymoon period. Hagopian estimates that it might be anywhere between 10% and 25% of the million or so beta cells the patient started with. What is certain is that some beta cell function persists. Whatever their actual number, the remaining beta cells continue to help regulate blood glucose, so Hagopian and his colleagues are trying to keep them functioning as long as possible, perhaps forever.

"This is a very exciting prospect," he explains. "We're trying to prolong the honeymoon period. If a newly diagnosed patient still can produce at least some of his or her own insulin, that's a good thing. And if we can make that last longer—for a year, for two years, or more—that's even better."

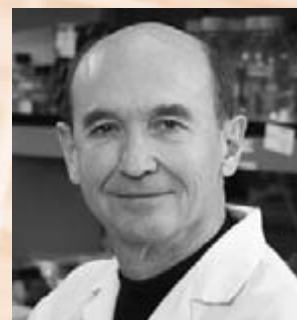
OKT3 and Immune Tolerance

The key to preventing and curing type 1 diabetes, according to Hagopian, is to create "immune tolerance." Many other approaches to containing diabetes are being explored by scientists, but they are

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PERSPECTIVES

by R. Paul Robertson, MD

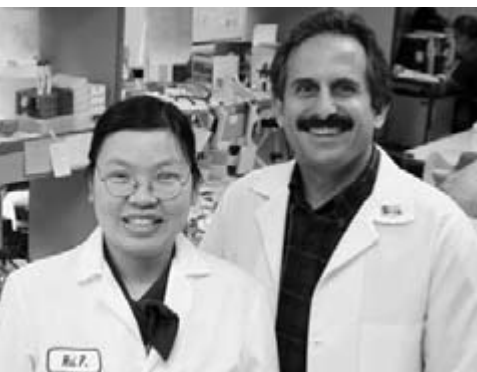


Listening to Patients

As a young boy I noted my father had a sign on his desk. On the side facing out it read "Frank O. Robertson, MD." On the side facing him it read "Shut up and listen to the patient. He's giving you the diagnosis." Now, THAT was a sign of the times. He routinely spent an hour with a single patient if he chose to, a privilege denied today's physicians.

While reading this issue of *The Laser*, listen to Carol Heimkes tell her story about the ravages visited on her by diabetes. It is a story filled with angst and success. It is a tale that was answered by unconditional love from her family and by Carol's undying dedication to help conquer this disease. And there is an unusual twist. Carol's sister Barb donated half of her pancreas to Carol for a transplant. Did you read (hear) this correctly? Barb donated half her pancreas to Carol, and Barb is OK? Yes, she has done fine and is living proof that we can get by with half a healthy

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Dr. Bill Hagopian and Dr. Hui Peng, scientists leading PNRI's OKT3 study

expected, it will provide type 1 diabetes patients with greater glucose control and less risk of diabetes-related complications than has ever been possible before. And the hope researchers are harboring is that the new drug treatment may do even more.

The Honeymoon Period

Type 1 diabetes is an autoimmune disease in which the immune system destroys all the body's beta cells, the cells in the pancreas that produce insulin. This immune destruction takes place over a considerable time. Its damaging work goes largely unnoticed because a healthy pancreas has hundreds of thousands of beta cells more than are needed to provide the body with all the

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MARCH 2006

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FROM THE EDITOR:

The Faces of Diabetes

by Rich Murphy

Diabetes is a silent disease. It ravages patients, families, and communities without calling attention to itself. It is often unreported as a cause of death, making way instead for the more familiar critical health threats of heart disease, stroke, and kidney failure. Compared to these, diabetes can seem benign, little more than an inconvenience for the most part, certainly manageable, even avoidable.

If we are going to contain and conquer it, however, we need to see diabetes for what it is—a chronic disease with still elusive causes and often wretched consequences. It is a plague, befalling some individuals and families, some racial and ethnic populations more fiercely than others for reasons we still don't understand. Over time for many of its patients, it brings in its wake a trail of grief and suffering, lost work, persistent debilitation, huge costs, and no reversal.

PNRI's mission is to eliminate diabetes. Its scientific talent and resources are dedicat-

ed to precisely the most efficient location along the membrane of the cell for effective secretion. It targets the key proteins responsible for beta cell damage and death. It identifies and tracks the emergence of the special antibodies that signal immune attack on beta cells long before any symptoms of diabetes appear. All of these—and more—are the patient work of PNRI scientists, and the success of their efforts will be essential to the elimination of diabetes.

But when we focus in *The Laser* on the brilliant technical possibility that a monoclonal antibody, called OKT3, may be able to reset the immune system, block its attack on beta cells, and prolong insulin function, we need to remember that it is children and families who will benefit. The elegance of PNRI science is in the service of people.

To fully understand, therefore, what diabetes research is, and why it needs to be supported, we need to see the faces of diabetes.

...we need to remember that it is children and families who will benefit.

The elegance of PNRI science is in the service of people.

ed to this end, and it announces its commitment everywhere: "Preventing and Curing Diabetes."

Given the complexity of the problem, however, and the broad and urgent reach of its threat to public health here and around the world, the Institute recognizes that a concerted effort of many segments of society will be necessary to arrest its growth. PNRI's special contribution to this collective effort will be fundamental—the basic and clinical scientific research necessary to disclose the cellular and biochemical mechanisms of the disease and to block or reverse their corrosive course.

Such research is necessarily complex. It concerns, for example, the intricate but robust process by which insulin is synthesized and distributed. It studies the signaling mechanisms by which just the right amount

The face of Carol Heimkes, for instance, a member of PNRI's Board of Trustees, or of Bryan Bartley, a work study student in the Hagopian laboratory, or of Alma Rivera, a technician in the animal facility and in the Robertson group. The face of poet Katy Geibenhain, monitoring her glucose multiple times a day. The faces of the children and parents participating for years in PNRI clinical studies. And in the larger community around us, the faces of schoolteachers and lawyers, bureaucrats and clerks, police officers and doctors.

If we hope as a society to marshal the collective imagination and resources to combat diabetes seriously, we will need to be more aware of what it is and who diabetes research is for. We will need to look into the faces of diabetes.

Carol Heimkes: Doing Whatever You Can



Carol and Bill Heimkes

PNRI Trustee Carol Heimkes has battled diabetes for 45 years. She always thought diabetes only affected older people like her grandfather. However, when she was just a teenager, looking forward to Sorority Rush at the University of Washington, she collapsed at work. Her blood sugar was registered at 600. She was diagnosed with Juvenile Diabetes, and the devastating disease changed her life forever.

Carol began volunteering at PNRI three years ago. She first served on the *Evening of Wine* committee, then co-chaired the event. Last year she joined the Board of Trustees. She has been fundraising for diabetes research for almost two decades now, and she brings all of this development experience as well as boundless passion to PNRI. She brings the story of her struggle as well.

“Diabetes is a real challenge for anyone with this crippling disease,” Carol says. “It is a tough way to live, but you do whatever you can.” Her eyesight deteriorated rapidly as her diabetes progressed. She also developed kidney disease and neuropathy in her hands and feet. These serious com-

plications left her and her family little hope for a healthy future. Feeling hopeless, she decided to have a pancreas transplant, a procedure that was only possible because of a generous donor. “I was very blessed to have my sister Barb donate 40% of her pancreas to me,” Carol now says. Her sister gave her not only a new organ, she gave her strength. “Barb was the strong one who helped me get over my fear,” she explains, “not only for myself but for her health also. I could not lose her!”

“I never would have made it without the support of my husband of 42 years. He is a Godsend. He does everything for me that I can no longer do.” Bill and Carol have raised two children and now have four adorable grandchildren. Because she knows that during difficult times we need our family and friendships most, Carol is very appreciative. “I was lucky to have such a great support system through it all.”

Now her goal is to raise money for diabetes research, particularly the important scientific work underway at PNRI. It’s a fine coincidence that Dr. Paul Robertson, PNRI’s President and Scientific Director, was also the diabetes doctor who tended Carol and her sister through the pancreas transplant. Seeing what others have done throughout the years, seeing the doctors and volunteers, seeing the generosity and durable faith of her family—all of this, Carol says, “has touched my heart.” It has made her want to give more to research. “What better way to give than to help others (children and young adults) with diabetes. The challenges ahead of them can be huge. If I can help a little, it might make a difference.”

And she knows from experience how important that difference can be.

Glucose Self-Monitoring

by Katy Giebenhain

A stabbing in miniature, it is,
a tiny crime,
my own blood parceled
drop by drop and set
on the flickering tongue
of this machine.
It is the spout-punching of trees
for syrup new and smooth
and sweeter
than nature ever intended.
It is Sleeping Beauty’s curse
and fascination.
It is the dipstick measuring of oil
from the Buick’s throat,
the necessary maintenance.
It is every vampire movie ever made.
Hand, my martyr without lips,
my quiet cow,
I’ll milk your fingertips
for all they’re worth.
For what they’re worth.
Something like a harvest, it is,
a tiny crime.

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Join us in discovery

PNRI’s laboratories conduct pioneering research to prevent and cure diabetes. We invite your help to eliminate diabetes as a global threat.

BECOME A PARTNER IN DISCOVERY

Call or email Sheryl Stiefel,
Director of Development
206.726.1203 or
sstiefel@pnri.org
All inquiries are confidential.

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An Evening of Wine

flights of red & white

2006

Mark your calendars because the winery partners have been selected. The Save the Date cards have been mailed. And PNRI is building exciting relationships with new and returning sponsors and volunteers! Thursday, August 3, 2006, will be an evening of friends, food, and fine Washington wines.

So far, more than \$25,000 has been secured from An Evening of Wine sponsors – double from 2005 levels. This year's event

is being organized by PNRI's Wine Guild, co-chaired by Ryan Allison, founder of AWineStore.com, and Carol Heimkes, PNRI Trustee. Wine Guild membership is growing with participation from community volunteers and businessmen and women. Many opportunities remain to help with auction procurement, data entry, and the day of the event. For more information, call Shelby Clayton at 206.726.1200.

Sponsors

PNRI greatly appreciates the generosity of this year's sponsors of *An Evening of Wine*.

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Save the Date

Thursday
August 3, 2006
6:00 PM



Inspiring Partners: Low Impact Ideas with Fun Returns for PNRI

by Scott Hutchinson

The most common question in every non-profit is “How do we raise more money?” Often, this question leads to brainstorming, resulting in a golf tournament or an auction. As the event approaches, excitement builds along with the stress of staff organizers. Sometimes daily mission-work is slowed until after the fundraiser because there is not enough time to do both. Sound familiar?

Last fall, my friend Greg Pinneo approached me about this issue. His new company, Northwest Real Investors Association (www.nwria.com/community), believes in giving back to and reinvesting in our community. Greg knew my passion for PNRI, Seattle’s oldest medical research institute started by my grandfather, Dr. William Hutchinson, Sr. in 1956. He also knew my concerns about how non-profits have limited manpower to dedicate to events. Together, we came up with a solution: his company would host and staff an event with net proceeds donated to PNRI and Habitat for Humanity. Each organization provided marketing information to educate Greg’s philanthropy-giving audience. The results: at its first auction last December, 125 members and guests of NWRIA raised more than \$5,100 for PNRI! The event was fun and low impact on his (and PNRI’s) staff with a nice return on investment. This got me thinking; if PNRI had more outside events, they could generate more cash flow, raise more visibility, and cultivate more stakeholders to support diabetes research!

Third-party fund raising is common in Seattle. The hallmark of good third-party events is to keep it simple. For years, PNRI survived on donations from individuals and groups. As a friend of PNRI, I encourage you to help advance diabetes research by selecting PNRI as the beneficiary of your group’s next event. For more information about organizing your own third-party event, contact Sheryl Stiefel in the Development Office at PNRI or call 206.726.1203.

Would you like to support PNRI's mission to prevent and cure diabetes?

No matter the size, third-party or “outside” fundraising events help PNRI share its story to expanding audiences while raising funds for our acclaimed type 1 and type 2 diabetes research programs.

Throw a party, organize a race, coordinate a holiday drive at your office, and more....

You can raise critical dollars for PNRI by putting together your own special event to help conquer diabetes. Make it as large or as small as you would like; the only limit is your imagination. Examples of recent third-party events that support diabetes research at PNRI are:

- *Donn E. Owens Memorial Poker Tournament* – Since 2004, “Friends of Donn E. Owens” honor the memory of their dear friend by hosting an annual poker tournament. All proceeds support diabetes research at PNRI.



Seward Park Walkers

- *Seward Park Walkers* – In the mid-1960s, Charlotte Hutchinson, wife of then-PNRI President Dr. Bill Hutchinson, Sr., and others gathered every weekday to walk the paths of Seward Park. Often at the end of a walk, participants gathered for coffee and collected money for occasions of joy or sorrow. The Walkers always wanted to pay tribute to a member or friend in lieu of sending flowers. Faithful forever, today’s walkers continue to gather rain-or-shine. And yes, philanthropy remains a goal, or as one member shares, “giant strides for research.”

PNRI Tribute Gifts

October 2005 through January 2006
(Tribute name is listed in bold)

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Our staff is available to assist you with Tribute Gifts. Call 206.726.1200 or make a donation online at www.pnri.org/howto-help/gifts.

Have you recently been diagnosed with type 1 diabetes?

A new research trial that hopes to prolong natural insulin production in people with recently diagnosed type 1 diabetes is occurring at PNRI.

Diabetes researchers at Columbia University and the University of California at San Francisco demonstrated success in preserving insulin cell capacity in newly diagnosed patients with type 1 diabetes. They used a new experimental drug called OKT3. People with diabetes who continue to make any insulin on their own will have an easier time keeping blood sugars close to normal. This in turn has been proven to lessen long-term complications associated with this disease. PNRI is one of 6 sites in the U.S. that is offering this research therapy.

The study is funded by the National Institutes of Health, and coordinated by the Immune Tolerance Network. Research participants will be treated at the University of Washington Clinical Research Center. There is no cost to research participants. The study is looking for very specific people to participate in this research:

- People diagnosed with type 1 diabetes **within the last 6 weeks;**
- People from 14 to 30 years of age;
- Other criteria also apply.

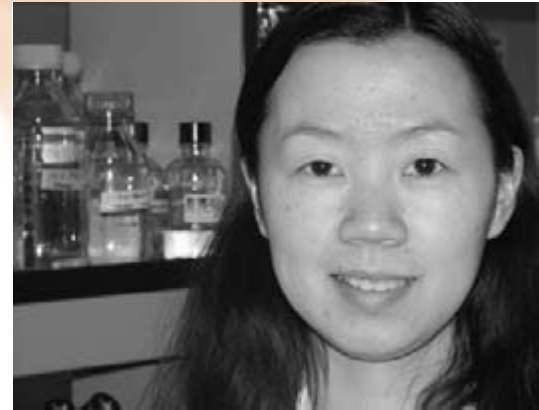
If you would like to hear more information about this research, please call Martha Pyne, MPH, Research Coordinator, toll free at 1-888-342-2140 or 206-568-1485, or email at mpyne@pnri.org (please note: the confidentiality of email communication cannot be guaranteed).

PNRI

National Recognition for PNRI Researcher Huarong Zhou

Dr. Huarong Zhou has won the 2006 Endocrinologist Award from the American Federation for Medical Research (AFMR). At the annual AFMR meeting this winter, she received the award, which recognizes her work on the mechanisms of pancreatic islet alpha cells.

Dr. Zhou's research investigates the relationship between alpha cells and beta cells in diabetes patients. Specifically, she is delineating the reasons why alpha cells do not function properly during periods of low blood sugar—"hypoglycemia"—in diabetes. Normally, alpha cells produce and secrete glucagon to compensate for low blood sugar by stimulated glucose production by the liver. But in diabetes that compensation process doesn't occur. According to Zhou's work, alpha cells need healthy beta cells—and the insulin those healthy cells regularly secrete—to function properly themselves. In their absence, alpha cells fail to function, and in the condition of



Dr. Huarong Zhou

hypoglycemia, this failure is so dangerous that it may lead to death.

Zhou is a post-doctoral fellow in the Robertson lab, where she has been conducting islet experiments since 2002. She holds both MD and PhD degrees from the Tongji Medical University in Wuhan, Hubei Province, China.

PERSPECTIVES

Listening to Patients

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pancreas and not develop diabetes, especially if we avoid getting obese in later life. Some people in medicine are outraged by the idea of living people donating pancreatic segments. But, if you listen to the donors, you will hear things like "Why not donate? It's OK to donate kidneys and segments of liver and lungs. Why not pancreas? And, besides, it's MY pancreas, not yours!"

In another part of *The Laser* read the poetry of Katy Giebenhain. Monitoring one's own glucose involves putting a drop of blood on a strip that goes into a machine that reads out the blood glucose level. The title of her poem is interesting. Glucose self-monitoring. In this poem, Katy appears to be monitoring self's attitude towards glucose monitoring with tongue in cheek. Why would she do this? The public press often portrays diabetic patients as "suffer-

ers" who must stick their fingers four times daily. What I hear Katy saying in her whimsy is not to take this so seriously. Self-glucose monitoring is a huge advantage for patients who in this era can actually determine the level of their glucose whenever they want, and thereby self-medicate themselves appropriately. This was not the case 25 years ago when only much less accurate urine-testing was available.

Listening to patients speak freely of their health experiences is an amazing opportunity doctors have to hear and learn. As patients tell their stories, they provide new and valuable clues to the unique forms that disease has taken in them individually. As we physicians listen, these clues can lead us to new appreciation of the causes of disease and guide us to new therapies for it. That's what the clinician-scientist does: listen, hear, learn, seek, find...on the road to conquering diabetes.

Giving Patients More Time

continued from page 1

peripheral to the central role of the immune system in the disease. The fundamental mechanism of type 1 diabetes is an immune attack on the body's own cells. Hagopian's goal is to understand and disable this process.

He and his team are working to create the conditions in which the immune system will tolerate its own cells as it is intended to, protecting rather than destroying them. The study underway now resets the immune system. It reprograms the system to suspend the attack it has mounted on the beta cells, perhaps to cancel its attack altogether.

Here's how it works. A specially engineered drug has been designed to intercede between the beta cells and the immune cells attacking them. Called technically OKT3, it is a monoclonal antibody. It binds to a particular receptor, CD3, on the surface of the immune cells and thus impedes their ability to attach to and destroy the beta cells. The actual mechanism of their disabling activity is still being worked out in detail by scientists, but the best current explanation is that they reprogram the immune system. They seem to regulate the ratio of different kinds of immune cells in such a way that the autoimmune attack is suspended. In effect, their binding to the immune cells delivers the message that the beta cells that were under attack are in fact OK, not to be targeted, not to be rejected.

Such an effect is still only transitory, however. In earlier studies, some time after

the one-time administration of the drug, the immune system mounted its attack again and sought out the remaining beta cells to finish them off. Though it had been possible to prolong insulin function for a while, the autoimmunity eventually returned and completed its destructive job. The purpose of this new study is to test whether a repeated dose of the OKT3 drug at the end of a year can push the resumption of the autoimmune attack out even further, and thus give type 1 diabetes patients even more time.

Promising Improved Diabetes Health

In the OKT3 clinical trial, 81 patients who have been diagnosed very recently—within the last 6 weeks—will be invited to participate at 6 different sites around the United States. 12 patients will participate in the PNRI trial here in Seattle. Some will receive the monoclonal antibody; some will not. The drug will be administered at the beginning of the first year of the study, then again a year later. Though its administration is limited to only two doses, its targeted effects on the immune system are expected to be durable. Hagopian's hope, and that of his colleagues, is that the study will show that the immune system may be able to be reprogrammed indefinitely and thus it may be possible to postpone forever the complete onset of type 1 diabetes.

What good would that do? It would permit patients to be able to continue producing their own insulin long after type 1 diabetes would normally have made this impossible. The immediate benefit is already clear. A person with type 1 diabetes who can still produce at least some of his or her own insulin has a much better chance of achieving good glucose control. As effective as exogenous insulin has come to be, patients depending entirely on external sources of insulin still have a difficult time managing their blood glucose levels.

Dr. Keven Herold, from Columbia University, one of the other scientists collaborating on the OKT3 study, explains why this matters. "Patients who have the ability to make any insulin on their own

can achieve much better glycemic control than those who don't." Even if they must embark on all the usual tasks of managing their diabetes—frequent blood testing, scrupulous insulin intake, careful diet monitoring—their own natural insulin function gives them a much better chance of maintaining healthy blood sugar levels.

This in turn, Hagopian adds, has huge benefits for patients. "Better control of glucose levels means fewer complications down the road." The secondary complications of diabetes all flow from sustained high levels of glucose in the blood. So the long-term benefit of prolonging normal insulin function is that it can reduce the risk of diabetes-related consequences like blindness, nerve damage, heart and kidney disease, and stroke.

Hagopian and his colleagues have crisply limited scientific goals in the OKT3 study. Extend immune tolerance for another limited period of time. Prolong beta cell function in increments. Know that better glycemic control for patients now will improve their current health. Trust that better control now will have a positive impact on the risk of future complications.

But they can hardly resist giving some voice to their hopes as well. They don't want just to treat type 1 diabetes. They want to prevent it. They want to cure it. If the honeymoon period can be prolonged for one year and then two, why not more? If for more, why not for life? Maybe OKT3—or some future refinement of it—can make the honeymoon last forever. If so, perhaps the beta cells that remain can proliferate and reverse the type 1 diabetes that has begun. And one more hope: if the immune system can be reprogrammed so that it stops an attack on the beta cells when they are almost gone, maybe it can be reprogrammed earlier, before the damage is extensive and before what we call type 1 diabetes can properly be said to exist.

For more information on the OKT3 study, contact Martha Pyne at 888-342-2140 or 206-568-1485 or mpyne@pnri.org

*They don't want just to treat type 1 diabetes.
They want to prevent it. They want to cure it.*

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THE LASER

MARCH 2006

Upcoming Events

Join PNRI in promoting diabetes research at two important gatherings this spring in Seattle.

DIABETES AWARENESS DAY

April 1, Saturday, 10:00-3:00

Bell Harbor International
Conference Center

Sponsored by the Juvenile Diabetes
Research Foundation

DIABETES EXPO

April 29, Saturday, 9:00-4:00

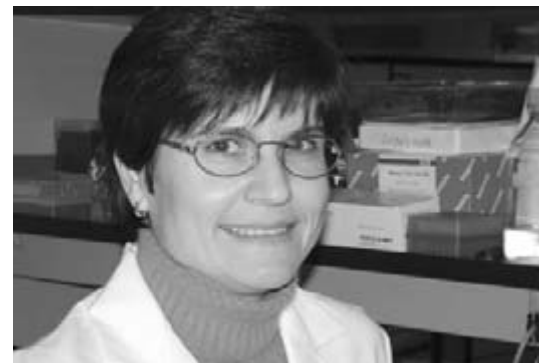
Qwest Field Event Center

Sponsored by the
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International Recognition for PNRI Researcher Marika Bogdani

On March 31 this year, Dr. Marika Bogdani will be in Belgium to receive the 2005 Sanofi-Aventis Award in Diabetes. The award recognizes the best scientific paper of the year in diabetes research in the opinion of a jury of judges of the European Association for the Study of Diabetes. The paper, published in *Diabetes* in December 2005, reports some of the work Dr. Bogdani has conducted on the conditions for growth of beta cells, a key area of research for the possible advancement of beta cell transplantation as an effective diabetes therapy. This award is not her first professional research recognition. In 2003, Dr. Bogdani also received the Best Paper Award in Basic Research from *Diabetologia* for a paper on human pancreatic ductal cells, which she published in that journal.

Dr. Bogdani, a post-doctoral research fellow in the PNRI laboratory of Dr. Paul Robertson, is a medical doctor with special



expertise in pathology. She received her PhD from the Diabetes Research Center at the Free University of Brussels under the direction of Dr. Danny Pipeleers. Currently, with the Robertson group, she is using morphology to study the effects of different treatment conditions on the development of type 1 diabetes. Her investigations are aimed at delaying the onset of the disease, attenuating its severity, or preventing it altogether.