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PNRI PACIFIC NORTHWEST RESEARCH INSTITUTE

THE LASER

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Inspiration: Catching Ovarian Cancer in Time

"She was my inspiration," Ingegerd Hellström says of the young scientific colleague who died in her mid-thirties from advanced ovarian cancer. Ever since that terrible event, Ingegerd has relentlessly worked to contain the disease. Recently she has made what looks like dramatic progress.

Ingegerd Hellström

A team led by her and her husband Karl Erik Hellström—and also including scientists and clinicians from the Hutchinson Cancer Center, Swedish Hospital, and the University of Washington—has discovered two biomarkers that promise to help make reliable early diagnosis of ovarian cancer possible. If her young colleague had been able to recognize her disease in its earlier stages, she might still be alive today, working at a lab bench alongside Ingegerd.

The Special Challenge of Ovarian Cancer

More than twenty thousand women will be diagnosed with ovarian cancer this year. But this number doesn't tell the whole story. Ovarian cancer is especially insidious. For much of its development, it has no symptoms, so it is usually missed in its early stages. That means that many more women have the disease than know it. When it is discovered—in stage 3 or 4—it has established itself and spread so that it is almost always irreversible. Nearly three quarters of the new cases discovered this year will have progressed this far.

"A terrible disease," Ingegerd says, shaking her head, and thinking of all the women who have died. Nearly 14,000 in 2002, according to American Cancer Society estimates.

If some method were found to clinically detect ovarian cancer in its earlier stages, the prognosis for women would be greatly improved. This is exactly the goal Ingegerd has been working toward for a long time. With the discovery of mesothelin/MPF and HE4, she is hopeful that she and her colleagues may be going in the right direction to detect ovarian tumors before they grow and spread.

Practice and Research

Ingegerd's passionate, patient-inspired search is typical of PNRI's institutional commitment to health. From the Institute's start, its guiding mission has been to use research to enhance human health. Many of its principal researchers are, like Ingegerd, doctors as well as laboratory scientists. Two of them regularly minister to patients.

Ingegerd says of herself, "I always thought I'd become a clinician, but I remained a scientist." Still, it's the women

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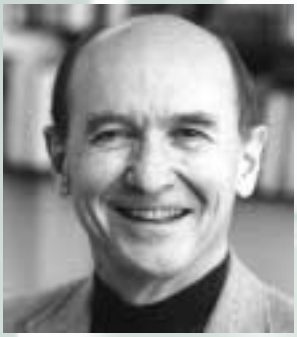
PERSPECTIVES

by R. Paul Robertson, M.D.



Silent Partners

Biomedical research more than anything else is a human enterprise. Much more a human enterprise than commercial businesses can aspire to be. The research bottom line is wonderfully different. It emphasizes knowledge gain rather than financial gain. Nonetheless, like all businesses, biomedical research requires husbanding of investments, careful expenditure of resources, and planning for unforeseen downfalls. And, like conventional businesses, we have our angels; our silent partners who rescue us when our research falters.

Who are these angels? Who are our silent partners who provide hope and help when progress flags, when despair sets in? Who provides the reservoir of optimism, born of their own needs, when things get out of joint and research goes awry?

They are not financial angels. It is true we often go hat in hand, pleading for funding of our research. We need financial resources to fuel

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THE LASER

FEBRUARY 2003

PNRI PACIFIC NORTHWEST RESEARCH INSTITUTE

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FROM THE EDITOR:

The Wit of PNRI

by Rich Murphy

Talking with Ingegerd Hellström and other PNRI scientists puts me in mind of Margaret Edson's 1999 Pulitzer Prize winning play, *Wit*. The main character of the play is an English professor. Her name is Vivian Bearing. She is middle-aged, single, severe, and a world authority on the 17th century metaphysical poetry of John Donne.

She also has ovarian cancer.

In the course of the play, she undergoes a radical experimental chemotherapy treatment. Because her cancer has already progressed so far, even this treatment is insufficient, and in the final scenes of the play, she dies.

Though sad, the play is also beautiful. It contains the contradiction, ambivalence, and humor of a metaphysical conceit. It leavens one woman's last months of suffering with courage and love. As Professor Bearing braces herself alone against the pain, she makes important discoveries about her life and builds a more humane relationship with her nurse than she ever allowed herself to establish with students.

The most provocative irony in *Wit* is that the distance between Professor Bearing and her students is re-enacted in the distance between her and her doctors. Absorbed as they are in their own scientific ends—the conquest of cancer, a prestigious grant, a national or international prize—the researchers who administer her ravaging treatment tend to see her as data. They want her to submit to the harshest therapy so they can see what will happen. They want her to live longer so they can take more measurements. At the heart of healing, the play suggests, lies a terrible contradiction.

But watching or reading the play, you can also see the achievement of PNRI researchers. Here at the Institute, they have joined empathy to imagination and intelligence. The most elusive and complex diseases take an awful toll in human suffering. They also provide—by reason of that very suffering—one of the greatest lures to scientific ingenuity. The chance to end such wretchedness has deep appeal. It inspires at once genius, creativity, and compassion. These are the motives that drive PNRI research.

The message of Margaret Edson's play is that the truest wit includes all three.

PERSPECTIVES

Silent Partners

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our creative fires as we pursue our dreams of discovery. Yet, the angels I refer to may or may not have money in hand to help us. But they always have much more invaluable assets to proffer, without our asking.

The women Ingegerd Hellström refers to in this issue of *The Laser* who have ovarian cancer typify these most valuable partners. Her patients drive Ingegerd in her relentless search for early diagnosis of the disease so they can be treated preventatively. Patients and their families are our most valuable silent partners, our angels. Their braveness and expectations of us are there to be seen in their hopeful and sometimes desperate eyes. Gazes that awaken Ingegerd and researchers just like her in early morning hours, thinking, what if…what if…. what if…

feature
Science in the Service of Health: a Prize-Winning Combination

Vincent Poitout in his lab

Even when PNRI scientists are writing grant applications, their passion for patients makes a difference.

Vincent Poitout says this is because when you're applying for a grant you need to show that the science is not only good but worthwhile. He should know. Poitout, one of PNRI's principal scientists, has just been named the 2003 Thomas R. Lee Award winner of the American Diabetes Association. The Lee Award recognizes the single most highly rated Career Development grant application throughout an entire year of nation-wide ADA funding cycles.

If you ask Vincent what led to his success, his first reply is the modest one: "Luck. Winning such recognition is due to so many factors," he says, "and the competing applications are all so good, that it almost doesn't make sense to call one 'best.'"

He may want to minimize the importance of his award, but Vincent is perfectly willing to admit that getting funded takes enormous work. And the key element of a successful grant application is the importance of the science it proposes.

The Big Picture

"One of the hardest parts of grant writing is always the same," Vincent says. "You must propose a very focused study on a very particular set of questions, which you demonstrate you can answer." You must limit yourself severely. "At the same time, you must show that what you want to do is significant. That it will help in the big picture."

For Poitout, the big picture is a worldwide epidemic of obesity and an alarming rise of type 2 diabetes among American youth. Not to mention the eleven million adults who already have been diagnosed with type 2 diabetes, as well as the estimated six or so million more who have the disease already but don't know it.

These numbers are not just the consequences of lifestyle changes, the product of a more sedentary culture with less healthy eating habits. They are a huge public health concern with enormous costs in dollars and suffering. Kidney disease, heart disease, blindness, nerve damage. These long-term terrible consequences of failing glucose control will now be even worse because young people with type 2 diabetes will have more time for them to develop and will encounter them at a much younger age.

So the big-picture task for diabetes research is to try to understand the mechanisms of glucose control in order to slow, stop, or reverse its failure. Only if scientists can achieve this understanding can the wretched toll of type 2 diabetes be reduced.

Vincent's particular focus is on fatty acids, what are called "lipids," and how they affect the function of beta cells. With the ADA grant, he is studying how fatty acids actually help beta cells produce insulin. He is exploring at least two possibilities. First, that fatty acids might activate a specific protein kinase, which would in turn stimulate an increase in insulin secretion. Second, that fatty acids might facilitate a process called protein acylation and thereby enable insulin secretion more effectively.

Clarity and Focus

But you don't win a national award, let alone get your application funded, by just having good ideas with significant consequences. You need to make those ideas crystal clear. They need to be original. You won't get funded if all you're proposing to do has already been done. Preliminary data must suggest that your approaches are promising. Further, you need to demonstrate that you can actually do the science. You won't get funded unless the reviewers are convinced you can actually do what you're proposing, that you can actually answer the questions you're asking.

"I'm a reviewer, too," Vincent says. "Being a reviewer has helped me enormously. I know how the process works. There's no shortage of good people. So I can see how I need to make the scientific case of my application rock solid."

This is why he gives himself time to write, maybe as much as three months to draft and revise a ten-page proposal. Changing his mind, filling holes in the reasoning, going back to the lab to try additional experiments.

But if you visit him during grant-writing time, you're less likely to find him in the lab than in his office. "You won't see much," he says, laughing apologetically and with some regret. "Just me sitting in front of my computer, looking at my screen, reading scientific articles, analyzing data, and writing."

The Prize

Still, the fundamental motive that drives him is that science has to matter to the lives and health of people. It's what Poitout said to the ADA. It's what he is saying to the American Heart Association in the grant proposal he's submitting now. The focus of his new study is the way a particular metabolite, "ceramide," inhibits insulin gene expression. But the big picture is heart disease. If he can help understand the mechanisms of diabetes, he can help reduce or eliminate one of the major causes of cardiac death.

That's the prize his eye is on.

in the service of health...

Leave a Legacy and Become a Partner in Discovery

If you have named Pacific Northwest Research Institute as a beneficiary of your estate, please let us know so we may recognize you as a Partner in Discovery. A bequest to support research at PNRI will leave a lasting legacy for future generations. In addition to bequests PNRI offers a full range of charitable giving opportunities, including:

- Closely held stock
- Beneficiary of a life insurance policy
- Charitable remainder unitrust
- Charitable gift annuities
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For information, contact us at 206.726.1203 or donations@pnri.org

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You can make your gift on-line at www.pnri.org. It takes only a few moments and your gift is complete. Your information is safe, secure, and confidential. Check it out!

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If you would like to receive your copy of *The Laser* electronically, just let us know. We can send your copy of PNRI's newsletter as a .pdf file, and all *The Laser* news, stories, research, and event announcements will come to you regularly via the internet. Just send your email address to info@pnri.org. Whether you prefer digital or the traditional print form, we hope that you will continue to share our news with colleagues, friends, and family.

Donor Appreciation Tea

supporters

Juanita Garrison (L), Charlotte Hutchinson (LC), Dr. Bill Hutchinson, Jr. (RC), Jermaine Magnuson

Ginny Anderson (L), Charlotte Hutchinson (C), and Esther Schaute (R)

PNRI thanked some of its most loyal supporters at the Garden Room of Seattle's Four Seasons Hotel in November. Charlotte Hutchinson, wife of PNRI founder, Dr. William B. Hutchinson served as Honorary Hostess. Friends of the Institute mingled with PNRI scientists and Board members, shared stories of PNRI's history, and heard Board of Trustees Chairman Bill Hutchinson and Scientific Director Paul Robertson celebrate our scientific achievement and promise. Linda Bonomi, Director of Development, reminded everyone how important private contributions are to PNRI's success, past and future. The tea was an opportunity to get some of the Institute's family together for a holiday celebration, but its principal purpose was to say thank you.

thank y

PROFILE:

profile

Bridget Dineen Haba

Bridget Dineen Haba joined PNRI as Administrative Coordinator of the Development team in October, 2002. Prior to joining PNRI, Bridget worked as Campaign Coordinator for Overlake Hospital Medical Center's capital campaign and for the United Way of King County's new business development team.

When asked about initial impressions of PNRI, Bridget responded, "It's amazing how passionate everyone at PNRI is about what we do here, and how their work, no matter if it is in a lab or in an office, contributes to the mission…*Preventing and curing diabetes and cancer.* That's a tremendous responsibility and a great challenge! In addition, I remember getting a hug from our CEO, Dr. Robertson, the second week I was here. He said, 'We give hugs here, it's like family'. I'll never forget that."

A Seattle native, Bridget graduated from Whitman College in Walla Walla, WA. In her free time outside of PNRI, Bridget, a recent bride, can be found with her husband, Matt, at the local wine shop looking for a new label to add to their collection, or at the nearest book store researching her next world travel adventure.

a future in which diabetes and cancer are history . . .

PNRI Tribute Gifts

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Mrs. Howardine M. McInnis

Matthew Gabrielson
Mr. and Mrs. H.G. Lewis

Funding PNRI's Mission

Out of every dollar brought into PNRI, eighty-two cents goes directly to research. The remaining eighteen cents is allocated for fundraising and administrative costs.

A top priority at PNRI is to maintain and grow the high quality of our research. Our scientists are nearly entirely self-supported through competitive grants which come from Federal, industry and private sources. But these funds do not cover all our needs.

Personal contributions are critical to PNRI. Over 6% of our $11 million budget comes from private donors. Their generosity helps to fund:

- Sophisticated research equipment and technology to keep pace with an ever changing environment
- Renovation of laboratory space to adapt to research requirements
- Start-up support to attract the brightest and most talented scientists
- Funding for pilot projects for promising new directions in research
- Training fellowships to support post doc fellows — young scientists still in training
- Interim funding to maintain the integrity of existing research awaiting approval of grant renewal application.

For more in-depth financial information about PNRI you can visit our website, **www.pnri.org/howtohelp/makeagift** and click on "View our IRS990 Form". This will immediately link you to Guidestar.com where you can look at our most recent IRS990 return. You can also contact us at **206.726.1200** and request an audited financial statement.

kudos

Institute Kudos

■ **Peter Dempsey, Ph.D.**
Peter Dempsey has received a new five-year National Institutes of Health (NIH) grant to study ErbB receptor signaling in beta-cell development and neogenesis. His goal is to better understand the role of betacellulin signaling in beta-cell biology. Such improved understanding will clarify the mechanisms of diabetes and advance the development of new therapies for the disease.

■ **William Hagopian, M.D., Ph.D.**
Bill Hagopian has been awarded a five-year, $1 million-a-year grant from the National Institute of Diabetes, Digestive, and Kidney Diseases. The grant will permit his lab to study the environmental triggers (e.g., infectious agents, stress, food, and chemicals) of type 1 diabetes in hundreds of young children.

■ **Senitiroh Hakomori, M.D., Ph.D.**
The Highly Cited Researchers Project of the Institute for Scientific Information (ISI) has designated Senitiroh Hakomori as one of their "Highly Cited Researchers" based on citations by other authors from 1981-1999. According to ISI, Hakomori's papers in Biology & Biochemistry received 8,435 citations.

COMMUNITY

community

PNRI Connects with the Community

Institute scientists have been taking lots of opportunities to tell community members about PNRI's work. In November, Scientific Director Paul Robertson addressed an overflow breakfast gathering of the Science and Technology Roundtable at the Rainier Club. More than seventy members and guests of the Technology Alliance attended. In what Roundtable organizer, Ann O'Donnell Bury, called a "fabulous" presentation, Paul reported on the latest progress of Seattle's islet transplantation consortium, and described some of the important challenges to this new technology for curing diabetes.

Melissa Smith, a post-doctoral fellow in Chris Rhodes's lab, and Peter Dempsey, a PNRI principal scientist, traveled to the Kitsap Peninsula in mid-November to address a luncheon meeting of the Kitsap County Diabetes Support Group. Peter and Melissa spoke about stem cells and their promising uses in diabetes research. Most of the audience members have diabetes or have family or friends with diabetes. They listened with lively attention, asking all sorts of questions and engaging the speakers long after the luncheon was over. So much so that Melissa remarked on the ferry ride home that they were "one of the most animated groups she had ever spoken with."

PNRI has also hosted the visits of several groups recently, to build relationships with them and to help them learn about our research. Representatives of the Project REACH coalition (Racial and Ethnic Approaches to Community Health) held one of their monthly meetings at the Institute. Vincent Poitout gave a brief summary presentation to orient them to the experimental work of his laboratory, then invited the group on a tour to discuss some of the ways PNRI scientists are trying to understand the mechanisms of type 2 diabetes. REACH participants were thrilled to be able to see the actual laboratories where the disease they are helping community members manage is being studied so intensively and with so much promise.

Students from Arlington High School also visited PNRI with their science teacher, Michele Wolski. They learned about how the types of diabetes are different and how researchers here at PNRI are developing experimental ways to prevent and cure them. Then they toured the Poitout lab to examine human islets and see the ways islets are cultured for research study. After returning to school, Ms. Wolski wrote that the "presentation on diabetes, the lab tour and conversations that followed, were informative and inspirational for these students. The experience you provided is of enormous value." It gave her students, she wrote, "exposure that is infinitely valuable."

Scientists from PNRI and its next-door neighbor, Seattle University, are building relationships, too. Many students from the university already work in Institute labs. Now their classroom teachers and their PNRI mentors are working more closely together to create greater learning opportunities for students and exciting research opportunities for faculty. A dozen members of the faculty from the departments of chemistry and biology, led by George Simmons, the Dean of Science and Engineering, met for lunch with PNRI Principal Investigators in December. They exchanged ideas about research and teaching and began to explore potential new ways to collaborate.

"It was fascinating! I got to see first hand research... [I]t was extremely informative...I loved it."

PNRI is committed to these many different kinds of public connections. The audience for its research findings is larger than the scientific community alone. It includes the rural school, the urban university, underserved neighborhoods, and the business and legal professions. All of these groups are made up of people for whom the prevention and cure of diabetes and cancer are a passionate and personal concern.

Catching Ovarian Cancer

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impact

who inspire her. She serves as a scientific resource for a group of ovarian cancer survivors who work together to advocate for advances in research to combat the disease. "They are great," she says, and then repeats, "great." But when the cancer recurs, as it often does, they also watch each other die. "What drives you," Ingegerd says, reflecting on their impact on her, "are those people who hope that you will make a difference for them." Such brutal facts of patient experience have been part of her scientific career from the beginning.

As a student at the Karolinska Institute in Stockholm, Ingegerd earned both an M.D. and a Ph.D. It was grueling training, she admits now without regret. She and her husband Karl Erik—also a student at the Karolinska, and also now a Principal Scientist at PNRI some forty years later—had two children while she was in medical school. They lived in a small apartment. The hours in the laboratory, classroom, library, and hospital seemed endless. Every second night she was on call for obstetrics. Ingegerd tells fondly of the toll of the work. She has a family photograph of herself at her desk late at night, the children in bed, with her books piled before her, and she sitting straight up in her chair, soundly asleep. But it was work she loved, and felt privileged to be pursuing.

She feels it still. Which is why one of the most durable memories she has of her ovarian cancer colleague is how the young woman continued to work faithfully at the laboratory, throughout her treatment, almost until her death. "She was . . ." Ingegerd searches for how to say it, "one of the bravest people I have ever known."

Hopeful Signs

The best diagnostic tool so far for detecting ovarian cancer—CA-125—is used primarily to monitor the progress of therapy in the treatment of the disease. It does not reliably identify ovarian cancer in its early stages.

But Ingegerd and her colleagues have discovered two additional markers, both of which seem helpful in detecting the cancer. Together, and perhaps in an inexpensive test which would combine them with CA-125, they might be useful in identifying more ovarian tumors.

The first of these markers is a molecule of the mesothelin/MPF family. Ingegerd's laboratory discovered that it is not, as was previously thought, membrane-bound in ovarian cancer cells. Instead, it is released into the circulation and is therefore detectable. It can be identified because it allows particular monoclonal antibodies (OV569 and 4H3) to bind to it. Ingegerd and her colleagues devised a test to determine the presence of such molecules in blood samples and found that the test repeatedly revealed their presence in the blood of patients with ovarian cancer.

A second marker is called HE4. It is a protein that occurs very frequently in ovarian tumors. With the help of a pair of antibodies that bind to it, the Hellström lab has been able to detect ovarian cancer in blood samples with a high degree of accuracy.

Making Discovery Count

The test for HE4 suggests that it is a more accurate indicator than CA-125 in distinguishing benign from malignant tumors. The clinical goal, therefore, is to try to develop a test that combines the different markers and that, with its increased sensitivity, can discover ovarian cancer earlier. Ingegerd and PNRI have entered into an agreement with a commercial cancer diagnosis developer—the Fujirebio Diagnostics Corporation, makers of the CA-125 test—to push the development of mesothelin/MPF and HE4 toward clinical use.

Fujirebio researchers are now consistently confirming Ingegerd's results. The next step will be for them to build a clinically useful test that searches blood samples for these telltale tumor markers. If they succeed, women and their doctors will be able to discover the presence of cancer while effective treatment is still possible.

And this is finally Ingegerd's hope—to get useful research results as soon as possible to the women who need them now. Before any more of the almost forty women a day die of the subtle and destructive disease they did not dream was there.

progress hopeful

kudos

Vincent Poitout, D.V.M., Ph.D.
Vincent Poitout has been named the winner of the 2003 Thomas R. Lee Award from the American Diabetes Association. The Lee Award recognizes the researcher whose Career Development grant application received the highest score from reviewers during an entire year of funding cycles.

Christopher Rhodes, Ph.D.
Chris Rhodes has received a five-year renewal of his NIH grant investigating the metabolic control of insulin exocytosis. He also was named a State of the Art Lecturer at the 38th Annual Meeting of the European Association for the Study of Diabetes (EASD) in Budapest, Hungary.

R. Paul Robertson, M.D.
Paul Robertson organized and chaired the 2nd Annual Symposium for Islet Transplantation at the Annenberg Center for Health Sciences. Researchers and clinicians from the U.S. and Canada gathered to discuss the progress of clinical trials, the use of stem cells and human beta cell lines, and other developments in the pioneering field of islet transplantation.

kudos

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THE LASER

FEBRUARY 2003

Archive help?

PNRI is collecting and organizing archival material from PNRF (our earlier name) during the years when Dr. William B. Hutchinson was the President and Director. We need a number of issues of the newsletter, called *Your Tomorrow*, from the years 1960-1985. If you happen to have any of those issues—or other PNRF materials that may be of archival interest and value—please contact Jean Pasche, PNRI Librarian, at 206.726.1200. We would love to have original documents and photographs, but we will gladly make copies and return the originals if you prefer. Thanks for your help!

HISTORY history

"The Doctor"

On the wall at PNRI hangs a large framed print of Sir Luke Fildes's famous 1891 oil painting, "The Doctor." It represents two of the principles that have guided the Institute since its start almost fifty years ago.

Care-givers need to know as much as they can about their patients and the disorders that afflict them. Researchers need to care about the patients for whose welfare they are gathering data and refining and testing hypotheses.

Fildes captured both these imperatives in his painting. With good reason. According to some historians, the painting grew out of a memory of the death of Fildes's own young son. In the light of imagination, the painter saw boy and doctor in a tableau of knowledge and love.

This is a retouched photograph of the color print hanging in PNRI's administrative offices.

The painting was a favorite of PNRI's founder, Dr. Bill Hutchinson. It—and the principles it makes vivid—are just part of his legacy to the Institute.