

THE LASER

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PNRI Lab Groups Cooperate
in Cancer Discovery

Ingegerd and Karl Erik Hellström and Jeff Ledbetter

Science by Collaboration

This is the constant theme of Karl Erik and Ingegerd Hellström, two of PNRI's principal investigators. Their recent cancer therapy collaboration with the Ledbetter lab at PNRI illustrates what they mean.

Along with Jeff and Martha Ledbetter, the Hellströms have created a gene that strengthens the immune system to fight cancer. It has been a joint effort, with important contributions from many individuals. Its success will be extended in turn by other scientists, here and elsewhere.

"There's very rarely such a thing as a completely original idea," Karl Erik insists. In most cases such a claim is false. Every scientific innovation builds on the work of others. Ingegerd agrees. "You can't specialize in everything. You must collaborate, especially if you want to take ideas from the laboratory to the clinic."

And they do. The Hellströms are interested in where ideas come from and in

where they go. Their goal is the health of very sick people whose lives they are trying to save.

Discovery

The Hellström-Ledbetter collaboration is reported in the latest issue of *Nature Medicine*. In a paper entitled "Gene therapy of cancer using single-chain Fv fragments specific for 4-1BB," the research team described a dramatic new cancer therapy technology. First they synthesized a gene so that it would cause particular biochemical receptors to appear on the surface of a tumor cell. Then they inserted this synthetic gene into tumor cells and injected the modified cells into laboratory mice that already had established tumors either in their lungs or skin. Most of the mice vaccinated by the altered gene became cancer free.

These results are remarkable. As Jeff Ledbetter says, cancer cells—especially in human cancers—are "incredibly clever." They evade detection by the immune system and thus proliferate unchecked. The mechanism the immune system normally uses to reject foreign cells isn't switched on with cancer because the surfaces of the cancer cells lack the structures needed to elicit a strong immune response. But if those cell surfaces can be altered to contain or mimic the triggering structures, they can lock onto, and destroy, the cancer.

"Nature has never done it this way," Jeff says, explaining the surface structures ("ligands") their synthetic gene promoted. "The artificial ligands we created are stronger and more active than natural

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PERSPECTIVES

by R. Paul Robertson, M.D.



No Firewalls at PNRI

Visitors' eyes widen as they enter the renovated 6th and 3rd floors of PNRI. Quilt patterns on the tile floor in front of the elevator door. Wide-open spaces with benches laden with instruments as far as you can see. Shafts of light coming through the east and west windows. Awesome views of the Cascade Mountains and Rainier. What once was a cluster of small, closed rooms gave way several years ago to tearing down of walls, brighter light sources, and openness. Now scientists from different teams intermingle throughout the day, sharing data and helping each other with complicated analytical machinery.

Life without firewalls at PNRI is more than just a physical fact. It is a metaphor for how we work. Roughly half of our scientists are focused on diabetes research, the other half on cancer research. Multiple collaborations exist between the teams of diabetes researchers as they

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THE LASER

MAY 2002

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Photo credits: Nancy Levine.



FROM THE EDITOR:

The Life of a Cell

by Rich Murphy

When asked about PNRI's community relations effort these days, I find myself listing a number of discrete initiatives. This *Laser*, for instance, and the Institute's evolving web site. Relationships with civic, corporate, and research partners in the Northwest. A developing media presence. Support for education and outreach programs, and participation in neighborhood and regional events. I explain how all of these depend on the energy and generosity of the people who work here.

But recently I've begun to think that I should start with mitochondria.

I first heard of these strange organelles twenty-five years ago. Lewis Thomas, then the president of the Memorial Sloan Kettering Cancer Center, published a collection of his *New England Journal of Medicine* essays in a book I assigned for an English course I was teaching. He called it *The Lives of a Cell*.

Then I heard about mitochondria again last week at a PNRI seminar conducted by visiting lecturer Michael Brownlee.

Mitochondria are just one of the components of the complex cellular system that creates and nourishes life. But the fact about them that especially appealed to Lewis Thomas is their independence. Having their own DNA, they appear to be partners of the cell, rather than parts of it. They seem to participate in an essential

collaboration with the cell in which they reside, like helpful guests.

Thomas's scientific mind was bemused by metaphor. So before I knew it he had used mitochondria to explain the social worlds of insects, the music of Bach, the infrastructure of human cities, the development of language, and the processes of science itself at a research laboratory.

Walk through the labs here at PNRI, and you'll see what Thomas meant. A host of scientists working independently. Doing their own experiments with discipline and precision, but then crossing lab boundaries and sharing instruments, supplies, ideas. Research teams meeting weekly to talk about their individual progress and help each other solve experimental problems. Two senior scientists pausing at the front desk in the lobby—interrupted on their way to the elevator—so engrossed in their shared insight they're taking notes on the ledge of the reception desk.

As professionally committed as Thomas was to biological research, it was the human system of cooperation that buoyed him about all this. The collaboration of outsiders, strangers even, helpful guests. The symbiosis of community relations, say, between a scientific institute and the society in which it lives. The more he thought about it, the richer he saw the application of cell biology to human life writ large.

*The other night [Lewis Thomas wrote]
driving through a hilly,
wooded part of southern New England,
I wondered . . . what is [the earth] like,
what is it most like?
Then, satisfactorily for that moment,
it came to me:
it is most like a single cell.*

Peter Dempsey, Cell Signals, and the Integrated Work of PNRI

“Cells need to understand their environment. They need to be able to monitor and respond to it.” This is how Peter Dempsey describes, in the most general terms, the work that has brought him to PNRI.

Peter is the newest principal investigator in the Institute. Elected unanimously by the other senior scientists here, he will establish a laboratory at PNRI to extend his study of the ways cells regulate their proliferation and differentiation. It is a line of research he has been pursuing for almost twenty years—at the Ludwig Institute in Melbourne, Sloan Kettering in New York City, Vanderbilt in Nashville, and now in Seattle.

Peter’s work will complement the research of other scientists at PNRI. It will also help answer the question most first-time visitors to the Institute ask: what is the connection between diabetes and cancer? Why, they ask, do you study both?

Communication

“It’s cellular communication,” Peter says, summarizing the focus of much PNRI research. The technical term for the general exchange of biochemical information is “receptor signal transduction”—the process



by which cells send signals to each other, receive and respond to signals from outside. Essentially it’s a process of communication.

Peter concentrates especially on the communication mechanisms of normal cells because, he explains, “only if we understand the way normal cell systems are regulated can we understand their dysregulation in the course of disease.” His work focuses on the interactions of membrane-bound growth factors and receptors on the surfaces of cells. When a protease (an enzyme) cuts a growth factor from the surface, releasing it into the local environment, the growth factor binds to a neighbor cell, is retrieved by receptors of the parent cell, or diffuses away to interact with other cells. This signaling process plays a fundamental role in the development, differentiation, proliferation, and survival of many tissues.

Cancer and Diabetes

What messages are delivered by the released growth factor? Which cell signals guide its course? How do cells respond to and communicate with their local environment? These are some of the questions scientists believe are key to understanding the mechanisms of both disease and health. They—and other questions like them—animate much of the research underway in PNRI labs. For Peter, the questions are fundamentally the same for diabetes and cancer.

“It’s only a model,” he acknowledges, pointing to his pencil sketch of cells and their surface molecules and their slender spiked prongs of growth factors and receptors. “It’s not all worked out.” But the evidence is pretty “tantalizing,” he says—from studies of the colon and the pancreas, from epithelial cells to beta cells—that all these signaling processes are alike.

It is that tantalizing similarity that makes PNRI’s association of cancer and diabetes labs a welcome new home for him.

PNRI Principal Investigators and their Major Areas of Research

- Peter Dempsey, Ph.D.
(Cellular communication, ErbB ligand trafficking and processing, disintegrin-metalloproteases, ErbB receptor signaling)
- William A. Hagopian, M.D., Ph.D.
(Type I diabetes mellitus)
- Sen-itiroh Hakomori, M.D., Ph.D.
(Aberrant cell recognition and signaling in cancer, based on changes in glycosylation)
- Ingegerd Hellström, M.D., Ph.D.
(Tumor immunology)
- Karl Erik Hellström, M.D., Ph.D.
(Tumor immunology)
- Michael Kahn, Ph.D.
(Chemical biology & functional genomics)
- Jeffrey A. Ledbetter, Ph.D.
(Cancer immunotherapy and T cell tolerance in autoimmune disease)
- Donald Malins, Ph.D., D.Sc.
(Breast, ovarian, prostate cancer)
- Vincent Poitout, D.V.M., Ph.D.
(Pancreatic beta-cell dysfunction in Type 2 diabetes)
- Christopher Rhodes, Ph.D.
(Biochemistry of pancreatic beta cells)
- R. Paul Robertson, M.D.
(Pancreas and islet transplantation, glucose toxicity of pancreatic beta cells)

science in the service of health...

PNRI

A National Program for the Conquest of Cancer



In 1970, Dr. William B. Hutchinson represented the Pacific Northwest Research Foundation on a historic U.S. Senate panel of cancer experts. The panel's report was titled *A National Program for the Conquest of Cancer* and led directly to the National Cancer Act of 1971. Hutchinson and his colleagues summarized the present state of scientific knowledge about cancer and drew up a broad and aggressive federal plan to attack the disease.

"Cancer is an implacable foe," the report read, "and the difficulty of eliminating it as a major disease must not be underestimated. . . . While it is probably unrealistic at this time to talk about the total elimination of cancer within a short period of time or to expect a single vaccine or cure that will eradicate the disease completely, [we believe] that an accelerated and intensified assault on cancer at this time will produce extraordinary rewards. The Committee is unanimously of the view that an effective national program for the conquest of cancer should be promptly initiated and relentlessly pursued" (p.8).

Lab Groups Cooperate

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ligands, so they trigger the immune system to destroy the cancer."

This success is particularly noteworthy for two reasons. First, the mouse cancer the Hellström-Ledbetter team studied is like human cancers in its elusiveness. It typically calls very little attention to itself, sending weak signals—or none at all—to the immune system. Second, once the immune system is activated by the artificial gene-encoded surface structures, it goes on to destroy even those natural tumor cells that lack the artificial ligands. This is important news for the field of immunotherapy.

Team Effort

But neither the Hellströms nor the Ledbetters could have done it alone. Karl Erik says, "It took a whole network of interactive people."

Immunologists have been working for a generation to understand the mechanisms of immune cells and disease. The therapeutic strategy of attacking cancer cells with cancer cells has been in development for many years. If the immune system can be induced to turn itself on in a regulated way, then it should be able to reject cancers before they metastasize in the body.

Some of the actual hands-on laboratory work of this latest PNRI discovery was done by Zhengmao Ye, the first author of the *Nature Medicine* paper and a post-doctoral fellow in the Hellström lab from the International Cancer Institute in Shanghai. He vaccinated the mice, monitored tumor development, summarized the data, and analyzed the mechanisms for tumor rejection. He was helped in this work by Amber Dahlin, a research technician in the Hellström group.

Ideas for building single-chain Fv (scFv) molecules, which represent the binding sites of antibodies, were introduced more than ten years ago. When the Ledbetters worked at Bristol-Meyers Squibb, they developed a technique for expression of such molecules at the cell surface. In the current experiments, Martha Ledbetter constructed the genes and transfected the

tumors. The Ledbetters' approach made it possible to use the antibodies to regulate immune response.

For the vaccine the Hellström-Ledbetter team was constructing, they chose molecules that could bind to the 4-1BB receptor on T cells and NK cells. This receptor was chosen because members of the team had earlier reported dramatic anti-tumor activity in mice that received the anti-4-1BB monoclonal antibody.

"You need to choose the right tumor," Ingegerd says. "Then you need to study it in the right way. All sorts of people contribute. You need it all in order to make the science work."

The Bigger Goal

The Hellströms have devoted their professional lives to an extremely complex problem—the diagnosis and cure of cancer—and its solution still eludes them. That, says Karl Erik, "is a humbling experience."

But as they talk about collaboration—about indebtedness, about needing others, about teaching and learning from them, about acknowledging and crediting their work—they grow more and more animated.

They are imagining the lives of men, women, and children now ravaged by cancer. They are thinking of patients diagnosed too late, families standing by through the terrible traumas of therapy, survivors supporting each other and advocating for more research, to bring cures closer, sooner.

It isn't diminishment the Hellströms feel. You can hear it in their voices as they talk. Impetuously they layer their memories of life and work, affirming each other's stories. They remember post-docs, quote Nobel laureates, explain the modified surface of that tumor cell they just altered, and remind you about the patients they hope to save.

It isn't diminishment you're hearing. It's passionate impatience. It sounds unmistakably like joy.

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



PROFILE:

Cynthia Jacobs: Building a Community of Ideas

Many Wednesdays just before noon in the Renshaw Room at PNRI, you'll find a buffet spread with refreshments. Cheese and olive pastries, chocolate and raisin cookies, an assortment of bottled juices, sodas, and coffee. In the back of the room, Cynthia Jacobs is sitting ready, next to the table with the laptop and the LCD projector. For almost three years now, along with many other responsibilities, Cynthia has coordinated the Institute's educational program of seminars and lectures. It is one of the richest elements of PNRI's community life.

"It's the opportunity to interact," Cynthia says, "that's most important. The chance to broaden the Institute's scientific base. The chance for people to collaborate together."

Throughout the year, scientists from across the US—sometimes from abroad—visit PNRI to share their latest research in public seminars. Sometimes, they talk about diabetes—about brain glucose metabolism, for example, or about the ways mitochondrial superoxide production helps explain the many complications of the disease. Sometimes, they talk about cancer—about dendritic cell-based tumor vaccines, or about hematopoietic cell transplantation. Once a year, a single scientist is chosen—for the sustained significance of his or her scientific research—to deliver the Langerhans-Virchow Lecture.

Cynthia orchestrates all these events. She manages the invitations, coordinates participants' travel, publicizes their topics, and—once the refreshments are set out and the chairs arranged—troubleshoots the projector to ensure that the speaker's slides work properly.

"I so admire these visiting scientists," she says with a smile and a characteristically vigorous nod of her head. (The gold dolphins at her ears bob exuberantly.) "I'm inspired by them. Scientists and doctors from all over the world. Each with a different perspective and background, each with a different story."

With such enthusiasm, it's clear that Cynthia is the right person to manage their visits. Her background helps, too. She studied communication in college. She worked for almost 20 years in clinical, research, and administrative settings at Children's Hospital—both in San Diego and in Seattle. There she provided direct support to the clinical staff, customer service to the families, and helped to coordinate the joint education program for doctors at Children's, the Fred Hutchinson Cancer Research Center, and the University of Washington.

Here at PNRI she continues that work. Hardly a week goes by without emails on everyone's screen announcing the next seminar. The website is regularly updated with current listings. Bulletin boards around the institute are covered with brightly colored fliers about aspartyl proteases and insulin granules. Renshaw Room chairs fill up as members of the audience balance plates, drinks and notebooks on their laps. Cynthia gives the speaker last-minute instructions on the remote control device and the laser pointer.

As the clock strikes noon, the exchange of ideas that's essential to science continues . . .

SPRING 2002 SEMINAR SERIES

Noon – 1:00pm
Renshaw Room
720 Broadway
Seattle, WA 98122

April 24, 2002

- Jamie Scott, MD, PhD
Simon Fraser University
Peptide Ligands for Neutralizing
Antibodies Against HIV-1

May 6, 2002

- Soldano Ferrone, MD, PhD
Rockwell Park Cancer Institute
HLA antigen defects in
melanoma. What have we
learned?

May 8, 2002

- Eugene Barrett, MD, PhD
University of Virginia
The Vascular Endothelial Cell –
A Target for Insulin Action

May 22, 2002

- Ercole Cavalieri, DSc
University of Nebraska
Medical Center
A Unified Mechanism in the
Initiation of Cancer and Other
Diseases by Catechol Quinones

June 5, 2002

- Vivienne Rebel, MD, PhD
Harvard University,
Dana Farber Cancer Institute
Divergent Roles for CBP and
p300 in Maintaining the
Hematopoietic Stem Cell Pool

interact
community

Hutchinson and Hagopian in Idaho

As this *Laser* issue was going to press, PNRI was visiting Boise, Idaho, with news about the latest developments in diabetes research. In a program hosted and orchestrated by PNRI Trustee John Hutchinson, four Boise audiences heard about important clinical and laboratory results for diabetes patients, their families, and their doctors.

Dr. Bill Hagopian, one of PNRI's principal investigators, told a general audience at St. Alphonsus Medical Center about cutting edge research in type 1 diabetes. An audience of doctors at St. Alphonsus heard Hagopian lecture on the prediction and pathogenesis of the type 1 disease. Allied health professionals gathered at the Humphrey Center for Diabetes Education in Boise to hear Bill survey the clinical applications of new research advances. Finally, the lecture tour ended at Boise's Arid Club, with a talk for interested community leaders on why we are at the brink of being able to prevent diabetes.

PNRI's outreach to communities takes many forms. This one—addressed to both the lay public and medical professionals—extends the knowledge of the Institute well beyond the laboratory bench. Hutchinson and Hagopian both know how important that is.

OUTREACH:

Team PNRI

PNRI has always played an active role in the local community. Its founders and scientific staff have contributed personally in multiple ways to the vitality of the city and the region. But recently, a number of PNRI staff have formed an organizing committee to sponsor Institute-community outreach with added focus and coordination. They've created Team PNRI, and they're inviting all Institute staff to join in—whenever, however, and to whatever extent they'd like. There are many ways to make a contribution to the community, and Team PNRI wants to welcome them all.

The first three community activities the organizing committee is promoting are the City of Seattle's Spring Clean, scheduled for Saturday May 4, the Beat the Bridge Run/Walk, scheduled for Sunday May 19, and the Race for the Cure, scheduled for June 2.

Spring Clean is being sponsored by the City of Seattle to involve residents in a cooperative effort to refresh the city's public spaces. Residents and businesses are being invited to clean up litter, plant trees, paint out graffiti, and improve streets and parks. Team PNRI will be helping out on May 4, in an effort coordinated by Elizabeth Oseid.

Beat the Bridge is dedicated to raising funds for diabetes research. Locally sponsored by Nordstrom, and held for 20 years here in Seattle, Beat the Bridge is one of a nationwide series of fund-raising events



Members of the organizing committee gather at Victoria's desk.

planned by the Juvenile Diabetes Research Foundation. PNRI participation in Beat the Bridge is being coordinated this year by Victoria Dobbins.

Race for the Cure is also a well-known local event. The Race welcomes walkers as well as runners in its effort to raise funds for the Susan G. Komen Breast Cancer Foundation. This year, Team PNRI will join in the Race with the helpful coordination of Institute librarian Jean Pasche.

The PNRI organizing committee is encouraging staff and family participation in all of these events. Bridge shoes and Race ribbons are showing up on walls all over the Institute. A distinctive Team PNRI t-shirt is being designed by Cynthia Kelp. We will be a visible presence on May 4, May 19 and June 2. We hope you'll join us. We want you on the team, too!

For more information on Team PNRI or any of these events, please call Elizabeth Oseid, Victoria Dobbins, or Jean Pasche at 206-726-1200.

Perspectives

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do between the teams of cancer researchers, somewhat contrary to the popular notion of competition in science. But even more impressively, virtually all of our scientific teams focused on either diabetes or cancer also interact with each other. This interactivity between disciplines makes for some precious moments at seminars when a cancer immunologist asks a diabetes biologist a question from a fresh point of view. After a pause, a catch of breath, and

some intellectual skirmishing, more than likely the two will get their heads together afterwards to think about a collaborative experiment. We've seen it happen many times in the past and I know we will continue to see it in the years ahead.

Firewalls are for insulation, insularity, and avoidance of heat. At PNRI, we eschew firewalls, preferring openness, thought-sharing, and the light that heat brings.

Partnerships

PNRI is actively cooperating with other Northwest organizations to serve the public and to advance biomedical research in the region.

- The Institute helped sponsor the 2002 Student Biotech Expo held March 1. Along with Immunex, Zymogenetics, SBRI, and a number of other for-profit and not-for-profit organizations, under the leadership of the Washington Biotechnology Foundation, PNRI helped fund and coordinate a science extravaganza for more than 200 local high school youth. Students from nine schools entered their work in a variety of competition areas, including molecular modeling, laboratory experiments, and science writing. The quality of the student work and the range and sophistication of their scientific interests impressed expert and lay visitors alike. Supporting such events is an important part of PNRI's commitment to science education.
- PNRI is working with a group of partners to advance public education about the nature and importance of clinical research. In addition to PNRI, the Partnership for Public Education includes representatives from the Washington Biotechnology and Biomedical Association, the Washington Association for Biomedical Research, the Fred Hutchinson Cancer Research Center, the Northwest Kidney Center, the Puget Sound Blood Center, Swedish Hospital, the University of Washington, Virginia Mason, and others. Together, these groups are building a media program and planning a lecture series designed to better inform the public about clinical research. PNRI's involvement in this effort is one way it can create productive relationships with other local research organizations.

- PNRI is participating in the REACH 2010 Coalition coordinated by the Seattle-King County Department of Public Health. Funded by the Centers for Disease Control as part of a national multi-site initiative, Project REACH is devoted to improving diabetes care in traditionally underserved racial and ethnic communities. Here in Seattle, REACH is serving African-American, Latino, and Asian communities with education programs and support groups to help diabetes patients better understand and manage the disease. PNRI is bringing a valuable research perspective to this vigorous public health initiative. At the same time, its involvement with the coalition adds an important community health dimension to the basic research of its labs.
- PNRI has joined forces with the Washington Association for Biomedical Research on two upcoming events. On May 17, PNRI will host WABR's annual essay contest awards ceremony for middle school students. Student finalists, along with their parents and teachers, will gather at PNRI for a morning of laboratory exploration under the guidance of Institute scientists, followed by a luncheon and presentation of awards. On May 30, PNRI will help sponsor a dinner with Lee Hartwell at the Bell Harbor Conference Center. Hartwell, winner of the 2001 Nobel Prize in Medicine, will talk about the personal dimensions of his scientific career. Proceeds from the Hartwell dinner will go to support teachers and students in WABR's science education programs.

Such collaborations happen only because of the dedicated hard work of PNRI staff. Credit is due here especially to Matt Donelan, Cynthia Kelp, Elizabeth Oseid, Jean Pasche, and Vincent Poitout.

PNRI Welcomes New Employees, Post Docs, and Visiting Scientists!

- Jin Suk Kang, Kahn Lab
- Hwang Jung Lim, Kahn Lab
- DeAnn Anderson, Hagopian Lab
- Yu Wei (Dick) Shen, Kahn Lab
- Kiara Held, Hellström Lab
- Hongtao Zhang, Hellström Lab
- Sandra Kanan, Hellström Lab
- Masayuki Ota, Hakomori Lab
- Natalia Utkina, Hakomori Lab
- Dane Miller, Kahn Lab
- Brendan Flynn, Hagopian Lab



New employees gather for a quick photo. Not shown are Kiara and Dane.



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THE **LASER**
MAY 2002

**PNRI
MISSION
STATEMENT**

The mission of the Pacific Northwest Research Institute is to prevent and cure cancer and diabetes and thereby help relieve human suffering.

Visit us on the web at:
www.pnri.org



YOU'RE INVITED:

Ralph Steinman and the Langerhans- Virchow Lecture

On Tuesday, May 21, Ralph Steinman will deliver PNRI's 2002 Langerhans-Virchow Lecture. Dr. Steinman is the Henry G. Kunkel Professor & Senior Physician in Cellular Physiology and Immunology at The Rockefeller University in New York. His topic will be "Dendritic Cells and the Control of Immunity and Tolerance."

Steinman has made profound contributions to science throughout an award-winning career. Most notably, he has elucidated the role of dendritic cells in antigen presen-

tation, which has helped explain immune responses to bacteria, viruses, cancer cells and allotransplants. Among other recognitions, he has received the Max Planck Award and the Robert Koch Prize. He is also a member of the National Academy of Sciences.

Dr. Steinman's lecture will be held in the Glaser Auditorium of Swedish Hospital in Seattle, beginning at 3:30 pm. Admission is free, the public is cordially invited to attend, and the lecture will be followed by a public reception at PNRI.

join us in discovery...