

GREETINGS FROM THE NFPTR TEAM!



NFPTR TEAM: Ms. Meghan Davis, Research Coordinator, Dr. Alison Klein, NFPTR Director and Ms. Diane Echavarría, NFPTR Coordinator

2009 has truly been another remarkable year for the NFPTR. First and foremost, we want to thank all of the families who make our research possible. This year marked the 15th anniversary of the NFPTR. We welcome all the new families and extend our continued gratitude to those families who have been with us over the past 15 years! The continued participation of our families and their willingness to stay in touch with us through email and though our newsletter update cards enables us to conduct studies such as our recent study looking at cancer risk in pancreatic cancer families discussed on page 3.

In 2009 we identified a new familial pancreatic cancer gene, *PALB2*, using a novel strategy to find genes responsible for inherited diseases (page 2). The discovery that inherited mutations in the *PALB2* can lead to the familial clustering of pancreatic cancer has opened many new arenas of research. One of these new avenues is new clinical trial, led by Dr. Michael Goggins. This study aims to target the biochemical pathway that is disrupted by mutations in *PALB2* and other related genes with chemotherapeutic agents that have been shown to exploit these particular defects (page 3). We hope this will result in a better gene-specific treatment response. In addition, our basic science researchers are hard at work following up additional leads generated through these projects that will hopefully lead to new ways to treat and detect pancreatic cancer early.

As always we work to better understand all aspects of pancreatic cancer. Dr. Chris Wolfgang, one of our expert pancreatic cancer surgeons who also heads a busy pancreatic cancer research lab is highlighted on page 3. One of his major areas of research is to

treat IPMN's a type of non-cancerous pancreas tumor that can progress to pancreatic cancer. His work parallels that of Drs. Hruban and Shi, described on page 2, to study the pancreatic pre-cancers. By gaining a better understanding of early pancreatic pre-cancers we hope that new early detection tools will be developed that can eventually lead us to ways to prevent pancreatic cancer from developing.

The research studies described in the newsletter are just some of our research highlights this year. We have had a very busy year! For more information about some of our other studies check out the "Pancreas Cancer News" section of our website as well as our publication list on page 4.

We always look forward to hearing from our NFPTR families, so please **return your update card** and feel free to contact us at 410-955-3502, or by email at pancreas@jhmi.edu throughout the year.

With appreciation and wishes for a safe and happy 2010.

Dr. Alison Klein, Director

PLEASE REMEMBER TO RETURN YOUR UPDATE CARD ENCLOSED WITH THIS NEWSLETTER. This information is very important to our research, even if there have been no changes in your family.
Thank you!

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Under a licensing agreement between Myriad Genetics Inc. and the Johns Hopkins University, Drs. Klein Eshleman, Hruban and Goggins, are entitled to a share of royalty received by the University on sales of products described in this newsletter. The terms of this arrangement are being managed by the Johns Hopkins University in accordance with its conflict of interest policies.

New Familial Pancreatic Cancer Gene Identified



Drs. Jim Eshelman, Alison Klein and Michael Goggins

A new pancreatic cancer susceptibility gene was identified this year, *PALB2*. This study was based on our completed pancreatic cancer genome sequencing project (see NFPTR News 2008) and published in the journal *Science*, in April 2009. Specifically, the team led by NFPTR Director, Dr. Alison Klein, reviewed all of the DNA sequences from an individual whose brother also had pancreatic cancer.

The team scanned all ~21,000 known protein-coding genes to find DNA variations in this individual. They then compared these variations found to those seen in healthy individuals to see if they could find the single DNA change, that caused this patient's cancer. After much work, this search resulted in the identification of the *PALB2* gene.

The team then looked for *PALB2* gene alterations in 96 other patients with familial pancreatic cancer, each of whom had at least one additional relative with pancreatic cancer. Three of these 96 individuals had similar DNA change, suggesting that about 3% of familial pancreatic cancer is due to inherited *PALB2* mutations. Interestingly, the *PALB2* protein binds to the *BRCA2* protein, the product of another breast and pancreatic cancer susceptibility gene. Learn more about *PALB2*, *BRCA2* and other causes of familial pancreatic cancer see our web site (<http://pathology.jhu.edu/pc/NFPTR/faq.php>).

We believe this is an exciting new finding which will help aid in the early detection through screening at risk individuals as part of ongoing early detection trials and better treatment of pancreatic cancers, such as those being studied in our new clinical trial on page 3.

Clinical Trial Targeting Pancreatic Cancer Gene Defects

Novel and rational therapies are desperately needed for pancreatic cancer and there are some promising therapies under investigation. Investigators are learning that there is variability in how pancreatic cancers respond to therapy and this is reflected in the DNA alterations that arise in pancreatic cancers. Our recently completed pancreatic cancer genome project highlighted the genetic variation among individual pancreatic cancers. These observations point to the particular need for personalized cancer therapy for patients with pancreatic cancer.

For example, in the laboratory we know that patients with pancreatic cancer who have inherited or acquired defects in the *BRCA2* gene and in other genes (such as *PALB2*) that repair certain types of DNA damage are exquisitely sensitive to drugs called "Parp" inhibitors. "Parp" is a DNA repair protein and Parp inhibitors work best in cancers that already have difficulties in repairing

DNA. Early clinical trials indicate that patients with *BRCA2* deficient cancers respond to the Parp inhibitor, olaparib. We are therefore initiating a clinical trial that will evaluate, olaparib with other drugs (irinotecan, cisplatin and mitomycin C) that also work in cancers that have difficulties in repairing DNA.

The trial is funded by the National Institutes of Health and the principal investigator is Dr. Michael Goggins, Professor of Pathology, Medicine and Oncology at Johns Hopkins. The lead oncologist at Johns Hopkins is Dr. Daniel Laheru, our expert pancreatic cancer oncologist. The clinical trial will also be opened at Columbia University, New York where Dr. Robert Fine is the lead investigator. Patients who are interested in enrolling in this trial should contact our clinical trial nurse coordinator, Rosalind Walker, RN, walker3@jhmi.edu.

Cancer Risk in Pancreatic Cancer Families

Our previous studies have clearly demonstrated that individuals with a family history of pancreatic cancer are at an increased risk of developing pancreatic cancer themselves and this risk increases as the number of family members they have with pancreatic cancer increases. This year, Drs. Li Wang and Alison Klein, examined if individuals with a family history of pancreatic cancer were at an increased risk of other cancers. They compared the number of individuals who died of cancer in NFPTR families to that expected in the average US population and found that NFPTR families were at an increased risk non-pancreatic cancer as well. Furthermore, individuals from families with

two or more pancreatic cancers had an increased risk of breast and ovarian cancers while individuals from families where a patient developed pancreatic cancer before the age of 50 had an increased risk of colon cancer. Individuals, with a strong family history of cancer, may want to seek out genetic counseling or talk with their physicians about their personal cancer risks. This work highlights the importance of regular screening for breast and colon cancer. Regular mammography and colonoscopy can detect early breast and colon cancers and reduces the chances of dying from these cancers.

Spotlight: Christopher Wolfgang, MD



Dr. Wolfgang runs a busy pancreatic surgery practice but he also spends a significant portion of his time conducting research to improve our understanding of the disease. Dr. Wolfgang's current research focuses on following three general areas of pancreatic cancer.

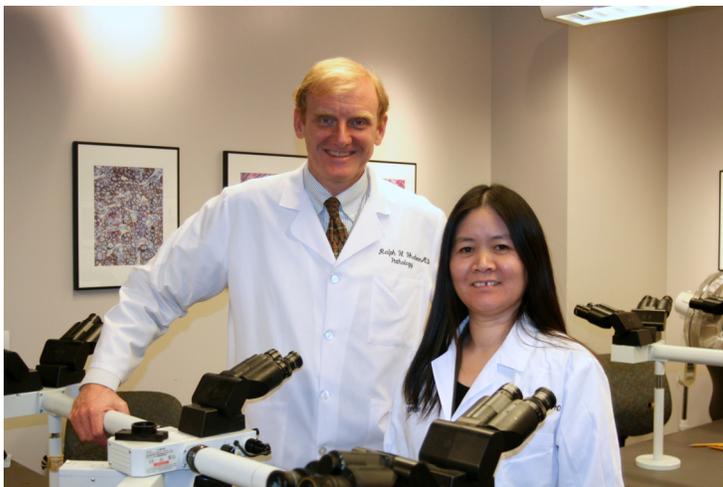
1) Clinical Research of Pancreas Tumors: Dr. Wolfgang studies numerous clinical aspects of pancreatic tumors. He has conducted studies that have described surgical outcomes in pancreatic cancer and specific precursors of pancreatic cancer, called Intraductal Papillary Mucinous Neoplasms (IPMNs). Moreover he has published studies on some of the more rare pancreatic tumors including solid pseudopapillary neoplasms (Franz's Tumors), acinar cell cancer and metastatic cancers to the pancreas. He is recognized as an expert on cystic lesions of the pancreas and is a member of the International Study Group of Cystic Pancreatic Neoplasms that establishes criteria for the management of these tumors (Sendai Criteria).

2) Safe and More Effective Chemotherapy for Pancreatic Cancer: Surgery for pancreatic surgery can now be done safely. The major limitation in curing patients of pancreas cancer following surgery is the high rate of distant (systemic) recurrence. Dr. Wolfgang is currently studying the importance of naturally occurring sterols (organic molecules from plants) in the regulation of pancreatic cancer growth. Through a better understanding of these compounds it is hoped that a safe and effective therapy that targets pancreatic cancer cells can be developed.

3) Early Molecular Events in the Development of Pancreatic Cancer: This project focuses on early molecular changes that occur when a normal pancreatic cell changes into a cancer cell. It appears that this process occurs through interactions between the functional cells of the pancreas (parenchyma) and the supporting cells (stroma). Dr. Wolfgang's lab has developed a system in which a thin section of a living pancreas can be maintained in vitro (in a Petri dish). Using this system, it is hoped pancreatic cancer may one day be prevented or least detected early.

Dr. Wolfgang can be contacted by email (cwolfo2@jhmi.edu) or office phone (410-502-4194). If you would like to make an appointment with Dr. Wolfgang, or one of the surgeons in his group, please call 410-933-PANC.

Understanding how Pancreatic Cancers Develop



Drs. Ralph Hruban and Chanjuan Shi

As part of our work to understand better how pancreatic cancers develop Drs. Chanjuan Shi, Alison Klein and Ralph Hruban examined the pancreas tissue of patients who underwent surgery for their cancers at Johns Hopkins. In many inherited cancer syndromes such as inherited colon cancer, patients with these syndromes

develop many precursor lesions or "pre-cancers" whereas from families with many in patients with the non-inherited cancers develop just a single pre-cancer that goes on to transform into a cancer. Based upon these studies, it is now routine for patients colon cancer to get frequent colonoscopies.

In the current study, the team compared the number of pancreatic cancer pre-cancers observed in familial pancreatic cancer patients (the pancreas of a patient who had other family members with pancreatic cancer) to the number of pancreatic cancer pre-cancers observed in non-familial pancreatic cancer patients (patients without a family history of pancreatic cancer). They observed that patients with familial pancreatic cancer not only had more pre-cancers but also more advanced pre-cancers than patients without a family history. Although there are no established recommendations for pancreatic cancer screening, even for patients from high-risk families, investigators are researching a number of new approaches. The findings from this new study will help form the basis for such tests. Our goal is to detect and remove curable pre-cancers before they grow into more difficult to treat pancreatic cancers.

HOW YOU CAN HELP:

Most importantly, please return your update card!

Spouses are eligible to donate a blood sample as a "control" (a person without pancreatic cancer to serve as a comparison) for our research studies. Contact us at pancreas@jhmi.edu.

Family members with *at least one first degree relative* with pancreatic cancer (sibling, parent, or child) *as well as one other family member with pancreatic cancer* are also eligible to donate a blood sample to aid our research. Contact us at pancreas@jhmi.edu.

Interested in Screening? Individuals with *at least two other family members with pancreas cancer* MAY be eligible for a research screening study (CAPS 4) using endoscopic ultrasound here at Hopkins. For information, please contact the study coordinators, Hilary Cosby or Verna Scheeler at caps4@jhmi.edu or 410-502-9795.

Also, remember to follow our research progress throughout the year and keep up to date on exciting news by checking the "Pancreas Cancer News" section of the Johns Hopkins Pancreatic Cancer Web: <http://pathology.jhu.edu/pancreas/>

MEDICAL DONATION RESEARCH PROGRAM

Dr. Iacobuzio-Donahue's Gastrointestinal Cancer Rapid Medical Donation Program (GICRMDP) continues to gather crucial information about metastatic gastrointestinal cancer by participants who volunteer prior to their death to undergo a rapid, research autopsy. If this research study is something you or a family member would like to learn more about, feel free to contact Dr. Iacobuzio-Donahue at ciacobu@jhmi.edu or call her at (410) 955-3511.

CERTIFICATE OF CONFIDENTIALITY

We want to remind the participants that the NFPTR continues to be protected by a Certificate of Confidentiality (NCI-01-062) from the National Institutes of Health, Department of Health and Human Services.

This certificate further helps us protect the confidential information that you have provided by giving us legal protection from having to involuntarily release any information about you. With this certificate, we cannot be forced by court order to disclose any information for criminal, administrative, legislative, or other proceedings.

If you have any questions regarding this certificate or would like a copy, please contact Diane Echavarría at 410-955-3502 or Dr. Klein at 410-955-3511.

LEARN MORE ABOUT OUR RESEARCH!

Below is a short bibliography of recently published research conducted by investigators working with the NFPTR. You can view abstracts of most or all of these articles by visiting www.pubmed.com and copying and pasting the title of article into the search field. If you have any questions about any of the studies discussed in this newsletter or listed here, please contact the NFPTR at 410-955-3502 or pancreas@jhmi.edu.

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CONTACT INFO

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