# GRANT SNAPSHOT

## 2003 Pancreatic Cancer Action Network – ASCO Career Development Award

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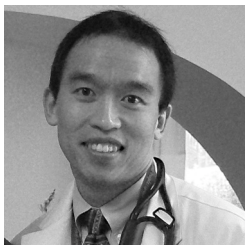
| Grantee: | Andrew H. Ko, MD |
| Institution: | University of California, San Francisco |
| Project Title: | *Detection, Analysis and Significance of Micrometastases in Pancreatic Cancer* |
| Award Period: | July 1, 2003 – June 30, 2005 |
| Amount: | $100,000 |



## Biographical Highlights

Dr. Ko is a specialist in gastrointestinal cancer, with a particular interest in pancreatic cancer and specifically the development of new treatment strategies, including molecularly targeted therapies. He earned his MD from The Johns Hopkins School of Medicine. After completing an internship and residency at Beth Israel Hospital/Harvard Medical School in Boston, he pursued a fellowship in medical oncology at Stanford University. Dr. Ko joined the University of California, San Francisco Medical Center in 2001, where he is currently an Assistant Clinical Professor in the Division of Hematology/Oncology.

## Project Description

The spread of cancer from the original tumor to other parts of the body is referred to as metastasis. Metastases may be visible via imaging tests such as CT scans. Very small metastases that are undetectable, such as individual cancer cells in the bloodstream, are called micrometastases (or circulating tumor cells). Dr. Ko's research involves collecting peripheral blood samples from patients with all stages of pancreatic cancer and analyzing them for the presence of these micrometastases. Measurement of these micrometastases may provide helpful prognostic and predictive information and could potentially be used to monitor a patient's response to treatment. Moreover, if enough micrometastases can be isolated, the genetic material could be analyzed for similarities and differences with tumor biopsy samples. Dr. Ko hopes that the study of these cells will yield clinically relevant information for treating and following patients, and that they will serve as surrogate tumor material (as they are more readily obtainable using noninvasive means) and help improve understanding of pancreatic tumor biology, mechanisms behind the spreading of pancreatic cancer, and drug sensitivity.

## Results/Outcomes

Several different technical approaches were used to look for and measure micrometastases in the peripheral blood of patients with all stages of pancreatic cancer, including immunomagnetic capture/flow cytometry and the commerically available Veridex CellSearch system. An initial pilot study that was conducted to assess the feasibility of this project revealed that 23 of 33 pancreatic cancer patients (69.7%) had detectable micrometastases, at a median concentraton of 1.1 cells

per mm3 of blood. This included patients with both early stage, resected pancreatic cancer as well as those with metastatic disease. Subsequently, as part of an investigator-initiated phase II trial for patients with previously untreated metastatic pancreatic cancer, a correlative study was built in which measured micrometastases at baseline,t two months, and six months after the start of treatment. Statistical tests were conducted to examine the association between concentration of micrometastases at each time point, and the change in concentration of these cells over time, with overall survival, time to disease progression, and tumor marker response. Final results indicated no statistically significant correlation between concentration of micrometastases at any time point and clinical endpoints. Change in cell concentration over time was also not associated with clinical outcomes. Another ongoing study for patients with previously treated metastatic pancreatic cancer is using a similar strategy, looking at both micrometastases as well as another type of cell called circulating endothelial cells, which may be a clinically relevant tool to use for monitoring.

## Lessons Learned

According to Dr. Ko, the care of patients with pancreatic cancer remains both extremely challenging and highly rewarding. The ability to conduct translational research that may ultimately prove beneficial for patients diagnosed with this disease involves not simply the study of interesting new therapeutic agents, but also discovery of new tools to help us better understand the biology of this disease. To accomplish this successfully, rich amounts of tumor tissue from patients are required for detailed genetic and molecular analyses. This has represented a longstanding difficult task for a variety of reasons: most patients do not have resectable disease, pancreatic tumor tissue is easily degradable, and for many patients, biopsy of a metastatic lesion is simply not technically or logistically feasible. This project has sought to overcome these hurdles by using a much easier, less invasive approach to isolate tumor cells from peripheral blood but, at least at this point, the concentration of cells remains too low to perform the types of analyses desired. Newer methods are needed to address this problem.

## Next Steps

While the feasibility of collecting micrometastases in patients with pancreatic cancer has been demonstrated, these cells are detectable at very low concentrations. It has not been possible to determine the prognostic and predictive significance of these cells in this disease, although this is being explored in ongoing studies.The ultimate goal remains molecular profiling of tumor tissue -- whether from micrometastases collected from peripheral blood samples or from tumor tissue directly acquired from the primary pancreatic tumor or metastatic sites -- and using this information to direct specific treatments for specific patients (so-called “personalized” medicine). With this goal in mind, Dr. Ko has since initiated a clinical trial for patients with previously untreated, metastatic pancreatic cancer that does mandate tumor tissue be obtained from each patient via core biopsy, prior to initiation of therapy. The tumor tissue is then processed to measure a number of candidate genes that may mediate sensitivity to different therapeutic agents, and is subjected to microarray analysis to look more broadly at genome-wide expression.

## Follow-Up Funding

Clinical Investigator Research Program Award, University of California, San Francisco Cancer Center/Mount Zion Health Fund (2003-2005).

NIH R01, Molecular Epidemiology of Pancreatic Cancer (2005-Present). (Co-Investigator)

National Comprehensive Cancer Network (2007). Pancreatic cancer clinical trial.

Multiple investigator-initiated trials relating to pancreatic cancer; studies ranging from 2003-present.

## Publications Related to Funded Project

Ko AH, Hwang J, Venook AP, Abbruzzese J, Bergsland EK, Tempero MA. Serum ca 19-9 response as a surrogate for clinical outcome in patients with advanced pancreatic cancer treated with fixed-dose rate gemcitabine. *Brit J Cancer*, 2005;93(2):195-199.

Ko AH, Tempero MA. The treatment of metastatic pancreatic cancer. *J Natl Compr Canc Netw*, 2005;3(5):627-636.

Ko AH, Tempero MA. Systemic therapy for pancreatic cancer. *Semin Radiat Oncol*, 2005;15(4):245-253.

Ko AH, Tempero MA. Monoclonal antibodies and other targeted therapies. In: Von Hoff DD, Evans DB, and Hruban RH, eds. *Pancreatic Cancer*. Boston: Jones and Bartlett, 2005.

Ko AH, Dito E, Schillinger B, Venook AP, Bergsland EK, Tempero MA. A phase II study of gemcitabine given at fixed-dose rate infusion in combination with low-dose cisplatin for metastatic adenocarcinoma of the pancreas. *J Clin Oncol*, 2006;24(3): 379-385.

Ko AH, Tempero MA. Pancreatic cancer: adjuvant therapy. In: McCulloch, P, Kerr, D, and Ajani, J, eds. *Gastrointestinal Oncology: Evidence and Analysis*. New York: Informa Healthcare USA, Inc., 2007.

Ko AH, Venook AP, Quivey J, Bergsland EK, Dito E, Schillinger B, Tempero MA. A phase II study of fixed-dose rate gemcitabine plus low dose cisplatin followed by consolidative chemoradiation for locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys*, 2007;68(3):809-816.

Ko AH, Scott J, Tempero MA, Park JW. Detection and significance of circulating tumor cells in patients with metastatic pancreatic cancer receiving systemic therapy. *J Clin Oncol*, 2007; 25(18S):4596. [abstract]

Ko AH, Wang F, Holly EA. Pancreatic cancer and medical history in a population-based case-control study in the San Francisco Bay Area, California. *Cancer Causes Control*, 2007;18(8):809-819.

Ko AH. Future strategies for targeted therapies and tailored patient management in pancreatic cancer. *Semin Oncol,* 2007;34(4):354-364.

Ko AH, Dito E, Schillinger B, Venook AP, Bergsland EK, Tempero MA. Excess toxicity associated with docetaxel and irinotecan in patients with metastatic, gemcitabine-refractory pancreatic cancer: results of a phase II study. *Cancer Invest*, 2008;26(1):47-52.

Wong D, Ko AH, Hwang J, Venook AP, Bergsland EK, Tempero, MA. Serum ca19-9 decline compared to radiographic response as a surrogate for clinical outcomes in patients with metastatic pancreatic cancer receiving fixed-dose rate gemcitabine. *Pancreas* (accepted for publication).