



**Research**

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## Consensus Report Offers Recommendations for Pancreatic Cancer Research Progress

In 2007, the National Cancer Institute convened the Clinical Trials Planning Meeting on Pancreas Cancer Treatment to bring together clinical, translational, and basic science investigators in pancreas cancer, and representatives from the patient advocacy community, pharmaceutical industry, and government agencies. The purpose of the meeting was to discuss ways to integrate current scientific knowledge into better clinical trial designs.

A consensus report from this meeting was published online in the *Journal of Clinical Oncology* in October, 2009\*. The report, written by lead author Dr. Philip Philip and numerous colleagues, outlines specific recommendations in the areas of drug targets, preclinical (laboratory) models to study pancreatic cancer, future clinical trials, biorepositories (tumor banks), and biomarkers.

### Targets

Mutations in the K-ras gene occur in more than 90% of pancreatic cancers, therefore making K-ras a popular target for potential therapies. However, the K-ras gene controls a complex series of cell signals and is difficult to effectively block. Despite these complexities, targeting K-ras remains a high priority, according to the report. Furthermore, numerous other tumor cell signaling targets are identified and suggested as priorities for further research, including: Raf, MEK, PI3-K, EGFR, IGF-1R, VEGF/VEGFR, HIF-1alpha, TGF-beta, and c-Met.

The report also identifies hedgehog, CXCR4, BMi-1, and Notch as targets for cancer stem cell signaling. Cancer stem cells are thought to be responsible for initiation and progression of tumors.

The final category of targets in the report relates to the tumor microenvironment - the cells, molecules, and blood vessels that surround and feed a tumor cell. Interactions between tumors and surrounding cells are not well understood in pancreatic cancer, though researchers believe these interactions are important and further research must be emphasized. Stellate cells signaling pathways, VEGF/VEGFR, CTLA-4, OX-40, PD-1 and VEGF, B7-H1/B7-H4, Tregs, MDSC, COX-2, and STATs were all listed as targets of interest in the microenvironment.

### Pre-clinical (laboratory) models

A variety of pre-clinical testing systems are available in pancreatic cancer, though according to the report, none has emerged as clearly superior. Scientists use genetically engineered mouse models, primary tumor xenografts (implanting human tumors in mice), and cell-based studies to help determine how therapies might work before testing in humans. The existing pre-clinical models each have their strengths and weaknesses.

The consensus report suggests further development and standardization of the preclinical models so that scientists can better test therapies in the laboratory and rationally design new treatments. This development and standardization is an important step in establishing reliable pre-clinical models that closely imitate human pancreatic cancer. The more strictly the pre-clinical models replicate human pancreatic cancer, the more likely studies using these models will accurately predict how effective treatments, imaging techniques, or early detection methods will be in humans.

### **Future clinical trials**

In recent years, the pancreatic cancer community has seen a number of large phase III clinical trials fail to demonstrate benefit for patients. Therefore, the consensus report states that “developing phase II trials that have a high chance of success in subsequent phase III testing is a major priority.” Several specific recommendations for the design of future clinical trials were outlined in the report.

The report suggests studying patients with locally advanced unresectable (not operable) disease separately from those with metastatic disease, and patients with unfavorable performance status separately from those with good performance status (a measure of the patient’s ability to perform daily activities). Furthermore, uniform eligibility criteria across phase II trials will aid in future comparisons of studies. By closely studying these groups of patients separately, true differences in response to treatment can be seen.

The report also recommends that for phase II and phase III clinical trials, overall survival should remain the primary end point, the main result that is measured at the end of a study to see if a particular treatment worked. Additionally, the report suggests that researchers consider clinical trials designed with multitargeted approaches based on scientific rationale, as well as trials with non-gemcitabine-based treatment combinations.

### **Tumor banks (biorepositories)**

The consensus report states, “One of the biggest barriers to conducting translational research in pancreatic ductal adenocarcinoma is the lack of appropriately collected, clinically and molecularly annotated, and properly stored biological material.” Many factors contribute to this lack of tissue available for study. However, the report offers the following recommendations to improve access to this resource: all randomized and selected single-arm clinical trials should consider inclusion of a biorepository, and infrastructure should be established to allow easy and shared use of this material.

### **Biomarkers**

Currently, no biomarkers for early detection or drug efficacy exist in pancreatic cancer. The report suggests that biomarkers should be tested in preclinical animal models and further evaluation should be part of future clinical trials in pancreatic cancer.

### **Conclusion**

Research progress has been made in understanding the molecular and genetic basis of pancreatic cancer, identifying potential therapeutic targets, and developing laboratory models of pancreatic cancer. This consensus report suggests thorough investigation of the identified targets and molecular pathways, as well as standardization of pre-clinical models. As these steps are successfully undertaken, researchers will gain greater understanding of the disease and the ability to design and test therapies with higher chances of benefitting patients. Future clinical trials should be based on this scientific knowledge.

*The Pancreatic Cancer Action Network continues to work in the scientific community to facilitate collaborations amongst researchers and to accelerate progress for patients.*

\*Philip PA, Mooney M, Jaffe D, et al. Consensus Report of the National Cancer Institute Clinical Trials Planning Meeting on Pancreas Cancer Treatment. *J Clin Oncol.* 2009; 27: 5660-5669.