GRANT SNAPSHOT

2007 Samuel Stroum – Pancreatic Cancer Action Network – AACR Young Investigator Award

Grantee:	Hiroyuki Kashiwagi, MD
Institution:	Washington University, St. Louis, MO
Project Title:	*Targeted Delivery of Pro-Apoptotic Therapeutics in Pancreatic Cancer*
Award Period:	July 1, 2007 – June 30, 2008
Amount:	$35,000

Biographical Highlights

Dr. Kashiwagi earned his MD from Tokai University School of Medicine in Kanagawa, Japan and then continued there to complete a surgical residency and research scholarship in pathology. He then became an Assistant Professor in the Department of Surgery and an Attending Surgeon in the Tokai University Hospital in Isehara. He currently is pursuing a postdoctoral research fellowship at Washington University School of Medicine.

Project Description

The sigma-2 receptor is highly expressed in human and murine pancreatic cancers and has limited expression in normal tissues. Binding of selected ligands to the sigma-2 receptor has been shown to induce apoptosis (i.e., cell death) in vitro and in vivo in mouse models of pancreas cancer. In previous research, Dr. Kashiwagi explored the proapoptotic peptide, TAT-BH3, which was found to induce tumor apoptosis in pancreatic cancer cells. When intracellular BH3 peptide was delivered and the sigma-2 receptor was engaged, there was an additive effect and increased cell death. Dr. Kashiwagi and his colleagues have designed a novel dual domain construct based on the sigma-2 receptor ligand (SV119) and proapoptotic peptide BH3. They plan to explore the efficacy and toxicity of these dual domain peptides as single therapies, as potentiators of each other, and as part of standard therapies. The expectation is that this novel dual domain construct will selectively target pancreatic cancer, deliver its proapoptotic cargo selectively into the cancer cells (leading to cancer selective apoptosis) and be effective in augmenting standard therapies.

Results/Outcomes

The study demonstrated that the dual domain therapeutics, S2-BH3, caused significant, dose-dependent apoptosis in several pancreatic cancer cell lines. In contrast, the mutated, inactive peptide caused no appreciable apoptosis ($p<0.0001$). Treatment with SV119 induced a lower level of apoptosis, as did treatment with TAT-BH3. In competitive binding study, S2-BH3 showed higher specificity of sigma-2 receptor the same as Sigma-2 ligand, SV119. Systemic injection of S2-BH3 in the pancreas cancer model also showed tumor specificity by immunohistochemistry staining. No acute toxicity was appreciated by histological examination of all tissues or by serum biochemical analysis. Furthermore, seven days of systemic administration of S2-BH3 in tumor bearing mice

resulted in suppression of tumor growth and a survival benefit (p=0.002). Sigma-2 receptor-specific ligand (SV119) potentiates other therapies such as TRAIL or TAT-BH3 (experimental) and Gemzar or Paclitaxel (clinical) in pancreas cancer model. The apoptotic effect of SV119 was examined in several pancreas cancer cell lines in combination with other apoptosis inducers. Both experimental and clinical materials induced dose-dependent apoptosis in all cancer cell lines in vitro. Combinations demonstrated dramatic increases in apoptosis. Systemic therapy of SV119 in combination with Paclitaxel or Gemzar showed survival benefit in the model of pancreas cancer. These results mean S2-BH3 potentiates other conventional therapies.

Next Steps

Before clinical study, Dr. Kashiwagi will explore whether this novel therapeutic is efficacious not only as a single therapy but also as a sensitizer to standard therapies. The main objective is to further develop this novel therapeutic strategy for pancreas cancer based on the selective delivery of proapoptotic molecules using sigma-2 ligands. Other proapoptotic therapeutics are being examined, such as AKT inhibitor domain or SiRNA linking the targeting domain (sigma-2 ligand).

Publications Related to Funded Project

Kashiwagi H, Hawkins WG, et al. Selective sigma-2 ligands preferentially bind to pancreatic adenocarcinomas: applications in diagnostic imaging and therapy. *Mol Cancer*. 2007;6:48.

Kashiwagi H, Hawkins WG, et al. Sigma-2 receptor ligands potentiate other conventional therapies and improve survival in model of pancreas cancer. *Cancer Research* (under review).

Kashiwagi H, Hawkins WG, et al. Targeted delivery of proapoptotic therapeutics in pancreas cancer. *Cancer Research* (under review).