GRANT SNAPSHOT

2005 Skip Viragh – Pancreatic Cancer Action Network – AACR Career Development Award

Grantee:	William G. Hawkins, MD
Institution:	Washington University in St. Louis, MO
Project Title:	*Assessing the Ability of Regulatory T-Cell Depletion to Augment Xenogeneic DNA Vaccination Against Mesothelin as a Method to Overcome Immunologic Tolerance in a Murine Model of Pancreas Cancer*
Award Period:	July 1, 2005 – June 30, 2007
Amount:	$100,000

Biographical Highlights

Dr. Hawkins received his MD from State University of New York at Stony Brook and completed a surgical research fellowship at Memorial Sloan-Kettering Cancer Center in New York, a residency in surgery at Massachusetts General Hospital in Boston, and a surgical oncology fellowship at Memorial Sloan-Kettering Cancer Center. In 2005, he joined the Washington University in St. Louis School of Medicine, where he specializes in complex cancer surgery for primary and metastatic lesions of the pancreas, liver and stomach.

Project Description

In the body's normally functioning immune system, regulatory T-cells protect against autoimmunity by suppressing immune responses to self-antigens. In other words, T-cells protect against the body mounting an immune response on its own cells. However, when a tumor exists in the body, these T-cells may also prevent or lessen an anti-tumor immune response. Previous research with a mouse model of pancreatic cancer has shown that depleting regulatory T-cells produces a delay in tumor growth and a short survival advantage. The funded project aimed to combine the inhibition of T-cell function with a technique called DNA vaccination to result in improved immune response to a tumor. The target for the DNA vaccination was mesothelin, a cell-surface protein that is often expressed on the cells of pancreatic cancer. Some research studies have indicated that therapies directed against mesothelin are capable of reducing tumor growth. The function of mesothelin is unknown but it has been speculated that it may have a role in facilitating the metastatic process (the spreading of cancer). This study hypothesized that the DNA vaccination will work together with inhibition of regulatory T-cell function. The goal was to trigger an immune response to the tumor that is specific towards the protein mesothelin, thus resulting in slowed tumor growth. All aspects of this project were conducted in the laboratory, using mouse models of pancreatic cancer. If successful, this strategy was expected to be translatable into a human clinical trial.

Results/Outcomes

Findings show that DNA vaccination is able to elicit a measurable immune response against the mesothelin molecule and this immune response results in a prolonged survival in mice with pancreatic cancer. The response, while measurable, is not impressive enough to warrant moving the studied vaccines to a clinical trial without a strategy to boost the effects.

Strategies have continued to be pursued to enhance the immune response to active vaccinations and to reverse the effects of tumor induced regulatory T-cells. Preliminary data have been generated that combine the vaccines with a strategy to inhibit regulatory T-cells. A trial will first be conducted of the adjuvant strategy in humans as a single agent. If the adjuvant is not toxic in humans, plans are to proceed with a trial of active vaccination and the adjuvant inhibiting regulatory T-cells. Additionally, targeted molecular therapeutics have been developed which induce pancreas cancers to undergo natural cell death (apoptosis).The plan is to combine this strategy with the vaccination strategy in future trials.

Lessons Learned

According to Dr. Hawkins, persistence is critically important to success in investigating therapies for pancreatic cancer. He advices that “If you have an idea which you believe in, make sure that you explore every avenue. Pancreas cancers are very robust and hardy and, in my experience, combinations of multiple strategies seem to work much better then a single strategy alone. If your idea does not work alone consider trialing it in combination with another complementary strategy before you move on.”

Next Steps

Several therapies are currently being explored for the treatment of pancreas caner. In addition to waiting for FDA approval for a phase I clinical trial of a strategy to inhibit the immune suppression caused by pancreatic cancer, methods are being researched to improve DNA vaccines in animal models. Most promising is work that is being conducted to develop targeted molecular therapeutics, which was originally designed to complement the vaccine program, and has proven very successful on its own. Efforts are also underway to redesign compounds for increased efficacy and stability.

Follow-Up Funding

Dr. Hawkins states, “The Pancreatic Cancer Action Network Grant was my first grant and it really helped shape my career. The preliminary data obtained during the time I was supported by the award led to several publications and I was able to leverage that data to obtain additional funding from the Gateway Foundation, the American Cancer Society and from the US government.”

American Cancer Society (1/1/08 -12/31/13; Amount: $135,000/$675,000). Mentored Research Scholar Grant, Targeted Delivery of Pro-Apoptotic Therapeutics in Pancreatic Cancer.

VA Merit Award (4/1/09 – 3/31/12; Amount: $150,000/$450,000). Sigma-2 Targeted Molecular Therapeutics for Pancreatic Cancer.

G-07-019 Cancer Treatment Research Foundation (10/1/08 – 9/30/10; Amount: $210,471/ $256,526). Phase I Study of Soluble Lag-3 (Imp321) and Gemcitabine in Patients with Advanced Pancreas Cancer.

Siteman Cancer Center Pilot Feasibility Grant (7/1/08 – 6/30/09; Amount: $ 20,000). Novel TNF-Inducing Ligand (TRAIL) Constructs as a Platform for Tumor-Directed Therapy.

Publications Related to Funded Project

Strasberg SM, Linehan DC, Hawkins WG. Radical antegrade modular pancreatosplenectomy procedure for adenocarcinoma of the body and tail of the pancreas: ability to obtain negative tangential margins. *J Am Coll Surg*, 2007; 204(2):244-249.

Kashiwagi H, McDunn JE, Goedegebuure PS, Gaffney MC, Chang K, Trinkaus K, Piwnica-Worms D, Hotchkiss RS, Hawkins WG. TAT-bim induces extensive apoptosis in cancer cells. *Ann Surg Oncol*, 2007;14(5):1763-1771.

Pierce RA, Spitler JA, Hawkins WG, Strasberg SM, Linehan DC, Halpin VJ, Eagon JC, Brunt LM, Frisella MM, Matthews BD. Outcomes analysis of laparoscopic resection of pancreatic neoplasms. *Surg Endosc*, 2007;21:579-586.

Thaker RI, Matthews BD, Linehan DC, Strasberg SM, Eagon JC, Hawkins WG. Absorbable mesh reinforcement of a stapled pancreatic transection line reduces the leak rate with distal pancreatectomy. *J Gastrointest Surg*, 2007;11:59-65.

Kashiwagi H, McDunn JE, Simon Jr PO, Goedegebuure PS, Xu J, Jones L, Chang K, Johnston F, Trinkaus K, Hotchkiss RS, Mach RH, Hawkins WG. Selective sigma-2 ligands preferentially bind to pancreatic adenocarcinomas: applications in diagnostic imaging and therapy. *Molecular Cancer*, 2007;6:48.