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“Irreversible electroporation as an in situ vaccine for pancreatic cancer”

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SCIENTIFIC ABSTRACT

There is a pressing need to develop potent immunotherapeutic interventions in pancreatic ductal adenocarcinoma (PDAC). Irreversible electroporation (IRE) is a non-thermal method of inducing cell death without destruction of adjacent collagenous structures, and is currently being used clinically for selected patients with locally advanced PDAC. *Our hypothesis is that IRE can serve as an “in situ vaccine” to generate neoantigen-specific T cell responses, and that these responses can be augmented by overcoming immunosuppression.* We have developed an immunocompetent syngeneic pancreatic cancer mouse model of IRE. Our preliminary data suggest that IRE of a primary tumor induces a systemic immune response that prevents growth of a secondary tumor challenge. We propose to use this model to examine the role of neoantigen-specific T cell responses as well as the effects of IRE on the tumor microenvironment. We will attempt to augment IRE- induced neoantigen-specific T-cell responses in our mouse model using several available agents targeting inhibitory pathways, with the goal of translating one or more of these strategies to human patients as an adjuvant therapy to IRE within 2-3 years. The research team brings together complementary expertise in pancreatic cancer, surgery, immunology, and clinical trials, a combination that increases the likelihood of extramural research funding.

LAY ABSTRACT

Approximately 40,000 people are diagnosed with pancreatic cancer each year in this country. Unfortunately, most patients—even those with tumors that appear localized on imaging—will eventually develop distant metastatic disease. The goal of immunotherapy is to utilize the patient's immune system to reject the invading “foreign” tumor like an infection. “In situ vaccination” refers to approaches in which the tumor is made to appear more foreign to generate immune responses against it. Electroporation is a common laboratory technique in which electrical voltage is applied to cells to make holes for intracellular delivery of DNA and RNA. Irreversible electroporation (IRE) is a technique now being used clinically for localized tumors that cannot be removed surgically (locally advanced tumors). Our hypothesis is that IRE stimulates immune responses to tumor cells and that we can augment immune responses to IRE with immunotherapy. We will use mouse models of pancreatic cancer to evaluate the effects of IRE on the immune system. We will evaluate the combination of IRE with immunotherapy drugs that are already available as well as novel agents in development. We envision that this approach will increase the proportion of patients with localized disease who are cured. Since we have already started a clinical IRE program at UCSD, a clinical trial in which an immunotherapy drug is given during or after IRE as adjuvant therapy would likely be feasible within 2-3 years.