Susan G. Komen for the Cure
Research Grants – Fiscal Year 2011

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Tumor-selectively replicating retrovirus vectors for gene therapy of breast cancer CNS metastasis

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Grant Mechanism: Post Doctoral Fellowship - Translational Research

Fellow: Akihito Inagaki, PhD
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Research Focus: Treatment

Public Abstract:
Modified viruses can be used to infect tumor cells and alter the tumor cell to make anti-tumor proteins. Most researchers use virus that can infect and modify the tumor cell it enters, but cannot make more copies of itself to infect additional cells surrounding the original infected cell. This type of virus is called replication-incompetent virus. Use of replication-incompetent virus is considered safe because no additional virus, which potentially could get out of control, is generated inside of the tumor. However such therapies have been shown to have only limited beneficial effects, presumably because too many tumor cells never get infected. Newer approaches investigate the use of replication-competent viruses to achieve highly efficient gene transfer to tumors. A successfully infected tumor cell then itself becomes a virus-producing cell, sustaining further infection events even after initial administration. We propose here to use a type of replication-competent virus that only infects dividing cells, which therefore can be used advantageously in the setting of breast cancer that metastasizes to the brain, as the virus will infect the rapidly dividing breast cancer cells but not the normal brain cells, which do not divide. This virus will carry a gene that converts a non-toxic compound, called a 'pro-drug', into a chemotherapy drug that is toxic to the cancer cells. Because the replication-competent virus can spread to most of the cancer cells by making more copies of itself and keeping up with cancer cell proliferation, there is effective killing of the cancer cells. And because virus spread is limited only to cancer cells, the pro-drug conversion occurs only locally inside the infected cancer cells themselves, so there are no side effects to normal cells in the rest of the body. The use of such a replication-competent virus is potentially more risky but is well justified in clinical situations such as lethal brain tumors. In fact, our team of specialists in gene therapy, neurosurgery, and neuro-oncology, in collaboration with a biotech industry partner, has already assembled the expertise and resources needed to rapidly advance this gene therapy technology to the clinic, and has just initiated FDA-approved clinical trials this past year for glioblastoma, a primary cancer originating in the brain. We now propose that this same approach may be highly useful against the highly aggressive growth of metastatic breast cancer in the brain, which has few treatment options and has a dismal prognosis. To this end, in this project we are proposing to re-confirm that the virus can efficiently infect and spread through breast cancer cells in vitro and in vivo, and achieve effective killing of mammary tumors in the brain in animal models, as required by the FDA before clinical trials can be approved. Also, we will determine the minimum dose of virus that can achieve a significant therapeutic effect, and test the best route of administration for the virus. In the very first human clinical trials that have just been initiated this year to test this gene therapy technology in patients with primary brain cancer, the virus is being injected right into the center of the tumor. Yet,

breast cancer metastases are often found as multiple tumors in the brain and may be difficult to eliminate by locally-administered replication-competent virus alone. So in this project, we will also test whether it will be feasible, safe, and efficient to deliver the virus through the bloodstream into multiple tumors at once. The results from these studies will guide the design of future clinical trials that apply this gene therapy technology for the treatment of breast cancer metastases in the brain.

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