

PRECIS

According to 2002 statistics from the American Cancer Society, an estimated 203,500 women will be diagnosed and 39,600 women will die from breast cancer despite all current therapy. This proposal attempts to exploit an innovative approach to breast cancer gene therapy that exploits a naturally occurring physiologic process in humans. It combines an unconventional suicide gene effect (direct killing without the need for a prodrug or other exogenous co-factors) with an immune enhancement effect (improved tumor antigen presentation). The expression of the murine $\alpha(1,3)$ galactosyltransferase [$\alpha(1,3)$ GT] gene results in the cell surface expression of $\alpha(1,3)$ galactosyl epitopes (α gal) on membrane glycoproteins and glycolipids. These epitopes are the major target of the human hyperacute rejection response that occurs when organs are transplanted from nonprimate donor species. The $\alpha(1,3)$ GT expressed in human cells renders them susceptible to antibody (Ab) and complement-mediated cytolysis and results in rapid cell death. The anti-tumor effectiveness of $\alpha(1,3)$ GT gene therapy will be tested in a Phase I and II clinical trial in women with recurrent or refractory breast cancer.

STUDY DESIGN: Women with recurrent or refractory breast cancer who have failed at least one prior salvage therapy and have measurable disease are eligible. Allogeneic human breast cancer cells (both ER positive and ER negative cells) expressing the hyperacute α gal antigen will be injected in an attempt to break tumor tolerance. Patients who provide informed consent will receive subcutaneous injections of allogeneic, lethally irradiated HAB cells expressing α gal epitopes and then monitored for toxicity and for disease response. This trial is organized as a sequential Phase I and Phase II trial. In the Phase I portion, 3 patients will be enrolled at each dose escalation level if no significant toxicity is observed. In the phase II an additional 32 patients will be enrolled to evaluate for potential efficacy. The second stage will enroll 32 more patients at the highest dose for efficacy evaluation (35 total). So a total of 44 patients will be enrolled.