

## **Targeted destruction of prostate, breast, ovarian, and testicular cancer cells through their LH/CG receptors**

William Hansel and Carola Leuschner

Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, LA, 70808

In a series of in vitro and in vivo experiments involving 1630 nude mice, the concept has been established that prostate, breast, ovarian and testicular cancer cells that express LH/CG receptors can be targeted and destroyed by compounds consisting of a lytic peptide moiety and a 15-amino acid segment of the beta chain of CG. LH/CG receptor capacity was closely correlated with the toxicity of the targeting lytic peptide-CG conjugates. Data obtained in vitro established the validity of this concept, showed the strong specificities of the Hecate- $\beta$ CG, and Phor14 and Phor21- $\beta$ CG conjugates in killing cells that express functional LH/CG receptors and proved that the LH/CG receptor capacity is directly related to sensitivity to the drug. LH/CG receptors can be up-regulated in vitro or in vivo in prostate cancer cells by pretreatment with follicle stimulating hormone (FSH) or estradiol. In in vivo experiments, Hecate- $\beta$ CG, Phor14- $\beta$ CG, and Phor21- $\beta$ CG(ala) each caused highly significant reductions of tumor volume and tumor burden in nude mice bearing prostate or breast cancer xenografts and in rats bearing diethylstilbestiol/dimethylbenz(a) anthracene-induced mammary tumors. Hecate- $\beta$ CG treatment of ovarian cancer xenografts in nude female mice was marginally successful. In addition to regressing the primary tumors, the lytic peptide conjugates are highly effective in targeting and destroying disseminated breast cancer metastases in lymph nodes, bones, kidneys, lungs and other organs. Hecate and Phor14 alone, at micromolar concentrations, kill prostate and breast cancer cells in vitro but they have no effect in vivo in mice bearing human prostate or breast cancer xenografts and only a small effect on rats bearing diethylstilbestrol/dimethylbenz[a]anthracene induced rat mammary gland tumors. Lytic peptide conjugate treated mice had no tumors, or tumors composed largely of necrotic cells when examined histologically. Tumors of control mice contained viable tumor cells which invaded adjacent tissues. . The treatments did not affect vital organs or tissues, including heart, lung, liver, spleen, intestines, pancreas, brain or kidney. Only gonadal tissue showed impaired function due to the treatment; sperm production was inhibited and interstitial cells were damaged. Blood vessels within the tumors and in adjacent non-neoplastic tissues were not affected by any treatment. Treatment with lytic peptide conjugates did not alter counts of leukocytes, erythrocytes or platelets. Liver function was not altered. These membrane disrupting peptide conjugates are not hemolytic, they have low antigenicity and are rapidly metabolized in vivo. These findings suggest that lytic peptide-LH/CG conjugates may be effective in treating hormone independent breast, prostate, ovarian, and testicular cancers, their metastases and disseminated cells. The concept of lytic peptide conjugate treatment provides a new mechanism for specifically destroying tumor cell membranes, without destruction of vital organs.