TARGETED ONCOLYTIC PEPTIDE FOR TREATMENT OF OVARIAN CANCERS

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First generation targeted oncolytic peptides consisted of synthetic lytic peptides conjugated to human chorionic gonadotropin or LHRH [5-7]. They selectively kill cells that over-express hCG or LHRH receptors within hours of contact with the cells. The direct contact and interaction with the cancer cell membrane causes their disruption and cell death by necrosis [5-7]. Esperance Pharmaceuticals™ has developed a new generation of oncolytic peptides conjugated to LHRH, that targets xenografts of breast, ovary and prostate cancers in nude mice. EP-100 is a novel oncolytic peptide that selectively targets surface LHRH receptors. EP-100 has been tested extensively in vivo and in vitro and shows no adverse effects in various species when administered in repeated injections. EP-100 is a fast acting compound, that lacks hemolytic activity and is not immunogenic.

Results in vivo studies

1. To test in vitro efficacy of EP-100 in ovarian cancer cell lines
2. To test in vivo efficacy of EP-100 in an OvCaR-3 xenograft model

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Background

Traditional non-targeted treatments are often associated with serious side effects, are systemically active and do not discriminate between cancer and normal cells in vital organs. Further, patient’s tumors often develop multi-drug resistance and the recurrence of their cancers often presents a more aggressive form of the disease resulting in death.

An alternative approach under development by Esperance Pharmaceuticals for killing cancer cells involves oncolytic peptides that are linear, alpha helical, cationic and short that directly interact with negatively charged membranes resulting in cell death. Major advantages of membrane-disrupting peptides over traditional non-targeted treatments include the following. 1. Preferentially destroy negatively charged cells, such as cancer cells, while normal cells up to 50 times more sensitive to peptides compared to normal cells [1].

Materials & Methods

In vivo efficacy studies were conducted in 96 well plate format (10,000 cells/well). Human ovarian cancer cell lines OVCAR-3 (negative for LHRH receptors) and OVCAR-5 positive for LHRH receptors were incubated for 1, 3, 6 and 24 hours with EP-100 or CLIP-71 Cell viability was determined using formazan conversion assays. OVCAR-3 xenograft model: Nu/Nu female nude mice bearing OVCAR-3 xenografts. Treatment was initiated by injecting tumor cell suspension tolerated in 4 day and 4 with a tumor mass of 100-300 mg on day 5. The doses for the 3 xenograft experiments were 0.2, 0.3 and 2 mg/kg body weight, given as a bolus single intravenous injection via tail vein. Treatment groups included controls (10 mice each) injected with saline or CLIP71 (2 mg/kg), and EP-100 (0.02 mg/kg, 0.2 mg/kg, and 2 mg/kg). Treatment was continued for 10 days and saline controls were observed. A number of cancers over-express receptors for luteinizing hormone releasing hormone (LHRH), including breast, ovary, endometrial (80%), prostate (86 %), and pancreatic (68 %) cancer [4]. This high incidence of over-expression of LHRH receptors in a wide range of cancers provides the rationale for targeting these receptors.

References

2. Bechinger, Biochim Biophys Acta, 1462, 157-183, 1999
8. Gaworowska et al, Gynecol Oncol 85, 45-52, 2002

Conclusion

EP-100 selectively targets and kills cancer cells that over-express LHRH receptors. These data indicate that EP-100 is a potential therapy for multi-drug resistant ovarian cancers in humans.