THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

SANJIDA MAHJABEEN

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE

GRADUATE COLLEGE
Graduate Pharmaceuticals Sciences

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SHetA2 VAGINAL SUPPOSITORIES AS NOVEL TREATMENT FOR CERVICAL DYSPLASIA: FORMULATION OPTIMIZATION AND EXPLORATORY IND-ENABLING PRECLINICAL STUDIES

COMMITTEE IN CHARGE: Lucila Garcia-Contreras, PhD, Chair; Doris M. Benbrook, PhD; Nathan Shankar, PhD; Michael Ihnat, PhD; Stanley D. Kosanke, PhD

ABSTRACT: Cervical dysplasia induced by the human papilloma virus (HPV) unpredictably progresses to cervical cancer. Cervical cancer is the second most common form of gynecologic cancer worldwide, with a larger rate of patients in developing countries. Existing treatments for cervical dysplasia are invasive and result in a poor quality of life for the patients. Thus, an effective and affordable therapeutic option is needed to treat cervical dysplasia to prevent its progression to cervical cancer. SHetA2 is a novel chemotherapeutic agent with strong chemopreventive activity demonstrated in human cell-culture and murine HPV-induced tumors. Elevated cyclin D1 protein expression is found in dysplastic cells and SHetA2 acts by suppressing cyclin D1 and apoptosis which causes G1 cell cycle arrest; thus, cyclin D1 reduction can be used as pharmacodynamic endpoint. However, the potential efficacy of SHetA2 is limited by its low oral bioavailability caused by its poor aqueous solubility. We postulated that local delivery of SHetA2 at the cervix would overcome its limited oral bioavailability and maximize the drug concentration at the site of action.

In the first project of this dissertation, the quality by design (QbD) approach was employed to optimize the suppository formulation to meet all the quality control specifications that are outlined by the United States Pharmacopoeia for suppositories of human use. These included integrity and stability of the suppository at room temperature, content uniformity, disintegration/softening and weight variation. Preliminary proof-of concept studies demonstrated that the optimized SHetA2 vaginal suppository was able to achieved cervix concentrations that were significantly higher than the SHetA2 therapeutic concentration (4μM) in mice. These high drug concentrations induced a 9-fold decrease in the levels of cyclin D1 protein indicating a correlation of drug concentrations with the pharmacodynamic endpoint. However, a large variability was observed among in the SHetA2 concentrations among mice receiving the same dose, at the same time point. The second study of this dissertation determined that the extent of drug absorption in the cervix of FVB mice appears to be influenced by the stage of the estrus cycle. SHetA2 absorption and residence time in the cervix is maximized during diestrus stage, whereas the pharmacodynamics effects appear to be favored during estrus stage. Therefore, in the third and fourth studies of the dissertation, all mice were synchronized to the same estrus stage to minimize variability in drug absorption.

The third project determined the pharmacokinetics and pharmacodynamics of different doses of SHetA2 after vaginal administration and contrasted it with that after the conventional oral treatment. We determined that a dose as small as 15 mg/kg administered by the vaginal route was able to achieve and sustain therapeutic levels of SHetA2 for up to 48 hours whereas oral treatment with a 60 mg/kg suspension was not able to maintain the therapeutic concentration after 1 hour. A dose finding study employing 15, 30 and 60 mg/kg doses revealed that the dose of SHetA2 administered did not correlate with the maximum concentration or area under the curve versus time, suggesting that the drug absorption was not linear. Moreover, the lack of a linear effect was also observed in pharmacodynamics studies with cyclin D1 protein. This project determined that the 30 mg/kg dose was the most effective to maintain therapeutic levels of the drug for the longest period of time and resulted in the reduction of cyclin D1 levels for longer duration. Lastly, the fourth project evaluated the safety of multiple vaginal administrations of this optimum dose for treatment (30 mg/kg) and determined that there was no drug accumulation in gynecological tissues and there were no visible signs of toxicity, as demonstrated by the lack of behavioral changes, weight loss or local macroscopic and microscopic irritation. Multiple vagina administrations of SHetA2 suppositories were also able to maintain the desired pharmacodynamics effect throughout the period of the study. In conjunction, these studies provide evidence that treatment with a daily 30 mg/kg dose can be used safely and effectively to treat cervical dysplasia in the K14-HPV16 mouse model of cervical dysplasia.