

CRPV ANIMAL MODEL STUDY PROTOCOL

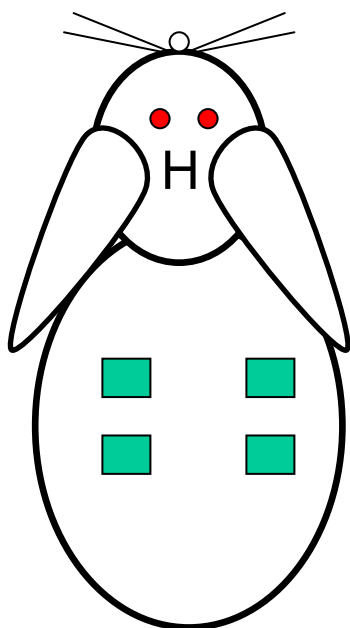
CATG Site Penn State College of Medicine

Study Title: Test of Compound X on rabbit papillomas

Study Design or Flow Diagram depicting study

Topical formulations of the compound X will be tested at three doses in groups of 5 rabbits at 4 sites per rabbit. One additional rabbit group will include a placebo treatment. Alternative deliveries include interalesional and systemic treatments depending on the nature of the compound to be tested (e.g. anti-viral, immunomodulator). The outline of the experimental procedure is as follows:

1. Adult New Zealand White rabbits will be purchased from CoVance, Inc., and will be of both genders.
2. Rabbits will be quarantined and cleared (14 days). Each rabbit will be inoculated with 10^{-2} wtCRPV (4 sites) CRPV stock.



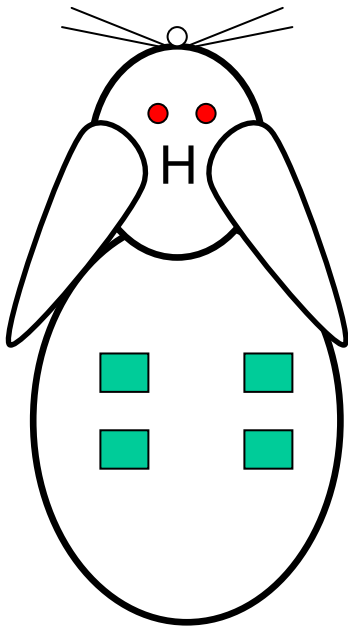
| <u>CRPV</u> | <u>Treatment</u> | <u>Treatment</u> |
|----------------------|------------------|------------------|
| 10^{-2} (wtCRPV) | L1 | R1 |
| 10^{-2} (mE8-CRPV) | L2 | R2 |

3. Combinations of L1, R1, L2 and R2 sites will receive treatments (see examples below).
4. The experiment will contain 20 rabbits. Most experiments include 5 groups of rabbits (Groups A-E)
5. A placebo group will serve as controls to assess local effects of treatment in treated Groups B to D. Vehicle will consist of placebo. Groups B-D will represent test compound comparisons vs placebo negative control. Doses of compounds will be chosen based on our previous observations and in consultation with Program Officer.
7. Treatments (topical) will begin at a time when the papillomas are visible but not greater

than a GMD of 5.0 mm. This time point will allow effects on visible papillomas to be assessed, and is the most clinically relevant situation. Treatment will be once weekly (Group B) 3X weekly (group C – MWF) and 5X weekly (MTWTF), for eight weeks with a dose of 0.1 ml per site. Alternatively, treatments may begin 14 days after infection at a time when there are no visible papillomas to maximize the effectiveness of the treatments. Body weights will be taken weekly, and sera collected at the end of the treatment period for blood chemistries as needed.

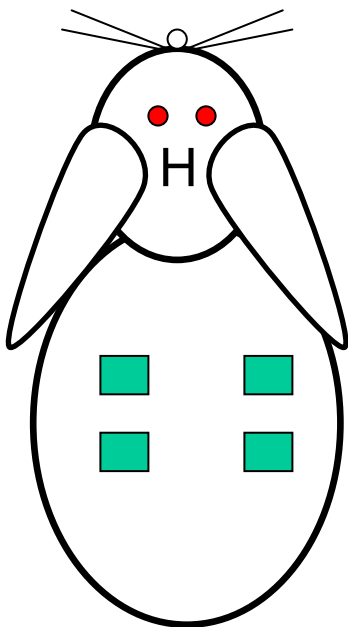
8. Papillomas will be measured weekly in 3 axes (length x width x height) in mm.
9. Data will be entered into a spread sheet and calculations conducted of the geometric mean diameter of each papilloma, mean \pm SEM for each group, Student's t-test between each paired groups and plots made of papilloma size vs time. Plots of weight changes are also conducted.
10. At termination, kidney and liver samples will be retrieved for histology and toxicity assessment. Skin/papilloma sites will be monitored photographically and biopsies assessed for histology at experiment/treatment termination. Serum samples can be collected to conduct blood chemistries to assess any toxicities of the compound under treatment.

Group A: all 4 sites = placebo ointment



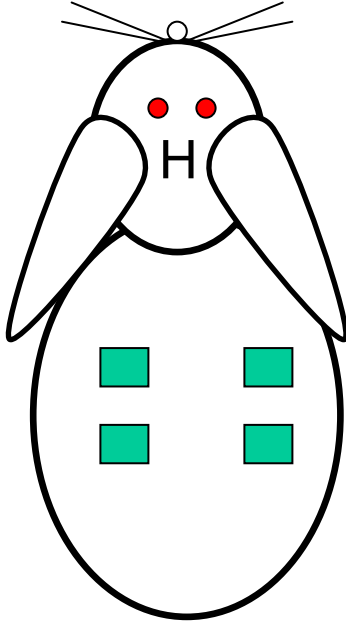
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| 10^{-2} (wtCRPV) | L1 | R1 |
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Group B: L1 and L2 = GS327422 (0.1%); R1 and R2 = GS327422 (0.03%) Treatments are once/week (Monday) for 8 weeks.



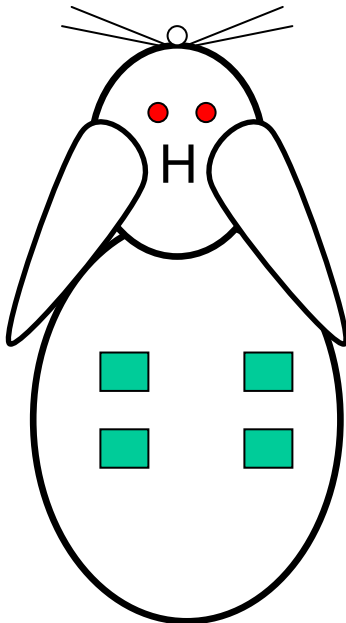
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|----------------------|------------------|------------------|
| 10^{-2} (wtCRPV) | L1 | R1 |
| 10^{-2} (mE8-CRPV) | L2 | R2 |

Group C: L1 and L2 = GS327422 (0.1%); R1 and R2 = GS327422 (0.03%) Treatments are three times/week (MWF) for 8 weeks.



| CRPV | Treatment | Treatment |
|----------------------|-----------|-----------|
| 10^{-2} (wtCRPV) | L1 | R1 |
| 10^{-2} (mE8-CRPV) | L2 | R2 |

Group D: L1 and L2 = GS327422 (0.1%); R1 and R2 = GS327422 (0.03%) Treatments are five times/week (MTWTF) for 8 weeks.



| CRPV | Treatment | Treatment |
|----------------------|-----------|-----------|
| 10^{-2} (wtCRPV) | L1 | R1 |
| 10^{-2} (mE8-CRPV) | L2 | R2 |