

OCT 13 2005

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UNITED STATES DEPARTMENT OF AGRICULTURE ANIMAL AND PLANT HEALTH INSPECTION SERVICE ANNUAL REPORT OF RESEARCH FACILITY (TYPE OR PRINT)	1. CERTIFICATE NUMBER: 35-R-0029 CUSTOMER NUMBER: 634	FORM APPROVED OMB NO. 0579-0036
Medical College Of Wisconsin Oscar F Peterson Animal Research Ctr 8701 Watertown Plank Road P.O. Box 26509 Milwaukee, WI 53226		

3. REPORTING FACILITY (List all locations where animals were housed or used in actual research, testing, or experimentation, or held for these purposes. Attach additional sheets if necessary)

FACILITY LOCATIONS (Sites) - See Attached Listing

REPORT OF ANIMALS USED BY OR UNDER CONTROL OF RESEARCH FACILITY (Attach additional sheets if necessary or use APHIS Form 7023A)

A. Animals Covered By The Animal Welfare Regulations	B. Number of animal being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not ye used for such purposes.	C. Number of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use o pain-relieving drugs.	D. Number of animals upon which experiments, teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals an for which appropriate anesthetic, analgesic, or tranquilizing drugs were used.	E. Number of animals upon which teaching, experiments, research, surgery or tests were conducted involving accompanying pain or distress to the animals and for wh the use of appropriate anesthetic, analgesic, or tranquiliz drugs would have adversely affected the procedures, res or interpretation of the teaching, research, experimen, surgery, or tests. (An explanation of the procedures producing pain or distress in these animals and the reast such drugs were not used must be attached to this report	F. TOTAL NUMBER OF ANIMALS (COLUMNS C + D + E)
4. Dogs			245		245
5. Cats			106		106
6. Guinea Pigs		610	42		652
7. Hamsters			268		268
8. Rabbits		4	658	10	672
9. Non-human Primates					0
10. Sheep					0
11. Pigs			7		7
12. Other Farm Animals					
Goats			21		21
13. Other Animals					
Chinchilla			36		36
Gerbils			20		20

ASSURANCE STATEMENTS

- 1) Professionally acceptable standards governing the care, treatment, and use of animals, including appropriate use of anesthetic, analgesic, and tranquilizing drugs, prior to, during, and following actual rese teaching, testing, surgery, or experimentation were followed by this research facility.
- 2) Each principal investigator has considered alternatives to painful procedures.
- 3) This facility is adhering to the standards and regulations under the Act, and it has required that exceptions to the standards and regulations be specified and explained by the principal investigator and ap Institutional Animal Care and Use Committee (IACUC). A summary of all such exceptions is attached to this annual report. In addition to identifying the IACUC-approved exceptions, this summary inc brief explanation of the exceptions, as well as the species and number of animals affected.
- 4) The attending veterinarian for this research facility has appropriate authority to ensure the provision of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use.

CERTIFICATION BY HEADQUARTERS RESEARCH FACILITY OFFICIAL
 (Chief Executive Officer or Legally Responsible Institutional Official)

SIGNATURE OF C.E.O. OR INSTITUTIONAL OFFICIAL	NAME & TITLE OF C.E.O. OR INSTITUTIONAL OFFICIAL (Type or Print)	DATE SIGNED
<div style="background-color: black; width: 100%; height: 20px; margin-bottom: 5px;"></div> (b)(6), (b)(7)c		10/6/05

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ANIMAL STUDIES

Approximately 400,000 cases of herpetic keratitis occur each year in the US. Some of these cases are due to initial infections of the cornea which can be treated with antiviral agents alone. Many of the cases, however, are due to recurrent disease which involves severe inflammation and an undesirable immune response, leading to corneal opacification ("stromal disease"). To reduce the risk of visual impairment, therapy including both an antiviral agent and corticosteroid is the standard of care. This form of therapy is successful only about 50% of the time and extended use of steroids causes many complications. The goal of these studies is to determine whether nitric oxide synthase 2 (an inducible enzyme involved in inflammation) plays a role in HSV-induced corneal edema. Our preliminary data indicate that it does. One of our aims is to determine whether NOS2 inhibitors are effective replacements for steroids.

Rabbits are the model of choice because herpetic keratitis in the rabbit mirrors the disease as it occurs in humans, including reactivation. Furthermore, rabbits have large corneas which are amenable to the evaluation of disease severity. This model has provided the preliminary data required to gain FDA approval of four antiviral agents for the treatment of acute disease. Models in mice, cats and guinea pigs have value for certain studies with other goals, but for the type of studies required to achieve our specific aims, rabbits are the best model.

Herpes simplex virus (HSV) is a neurotrophic virus which establishes latent infections in the neurons that serve the infected dermatome. HSV DNA also persists at the site of the initial infection. Primary infection will be established in rabbits by injection of 10⁸ pfu of virus at the midline of the alveolar mucosa of the mandible. These infections are much like primary infection in humans. The disease is a mild gingivitis, the rabbit seroconverts and a latent infection is established in the trigeminal ganglia. Three weeks after primary infection, 10³ pfu of virus is injected into the corneal stroma to produce stromal keratitis. At the time of both infections, rabbits will be anesthetized by IM injection of a mixture of 25 mg/kg ketamine and 5 mg/kg xalazine. One or two drops of 0.5% proparacaine will be placed at the site of infection. Some animals will be treated with antiviral agents combined with test compounds possessing putative anti-inflammatory activity. Other animals will receive no medication so that they can be killed at various times after infection and their tissues taken to the laboratory for analysis. The administration of any neuroactive drug other than ones used as part of a specifically-designed protocol could adversely affect the outcome of our studies.

The primary infection of rabbits rarely causes any problems in our hands. On rare occasion the primary disease can cause ulceration of the gingiva or death due to encephalitis just as it may in humans. The animals will be observed daily for signs of problems. Any animal experiencing severe oral infection or encephalitis will be killed immediately. We do not have exact numbers on these complications, but our guess is that less than 1% of animals experience such difficulties. The secondary or 'recurrent-like' infection of the cornea causes the development of herpetic keratitis and stromal disease. It is our experience that none of these animals will die of encephalitis because they all possess HSV-1 neutralizing antibodies from their primary infections. All of the animals, if not receiving antiviral/steroid therapy, will develop stromal disease which causes their corneas to become edematous and opaque, thus impairing vision. It

is our experience that only about 2% of eyes become blind. Rarely «1%) does bilateral blindness develop. If bilateral blindness develops, the rabbit will be killed immediately. If unilateral blindness develops, the rabbit remains able to function and eat, and thus is able to complete the experiment.