PROJECT DESCRIPTION

1 IDENTIFICATION AND SIGNIFICANCE OF THE INNOVATION

Advanced tools are needed for wirelessly and temporally controlled administration of drugs, toxins, neurotransmitters, and other biochemicals for investigation and/or treatment of diseased conditions. Only one in 10,000 drug candidates will successfully attain FDA approval[1]. Administration of new complex formulations is increasingly a limiting factor in the development process and inadequate lending to missed therapies. This unmet need is critically important in research involving laboratory animals, 95% of which are rodents[2]. Mice are most widely used given the availability of transgenic and knockout models.

Drug administration methods for mice are limited. Oral administration, typically by intragastric gavage[3], requires manual handling and restraint. Voluntary oral administration minimizes injury and reduces stress but is not accurate[4]. Intravenous and intraperitoneal methods require handling and needle injection. Repeated handling is labor-intensive, only suitable for intermittent administration[5], induces stress ("white coat" effects)[6], and can induce significant changes in physiologic parameters correlated with stress (concentrations of corticosterone, glucose, growth hormone, or prolactin, heart rate, blood pressure, and behavior)[6, 7]. In many regimens, chronic drug dosing is required and thus automation is desirable.

Continuous or automated chronic dosing is possible using a motor-driven infusion pump with a swivel-mounted catheter tether attached to the body via an implanted port. While handling is minimized, the catheter tether poses risks of infection and entanglement[8-11] and natural behaviors cannot be studied. Only a single animal can be housed per cage, contributing to the artificiality of the environment. Tethering impedes natural movement and thereby reshapes normal behavior. Abnormal animal responses include decreased exploratory activity, increased stereotypies, aggression and immobility, and altered stress hormone response[11, 12-16]. The sensitivity of drug administration to stress and environmental factors is well documented, motivating untethered, wireless chronic drug administration studies.

There are **no implantable pumps available for computer-controlled chronic dosing** in laboratory animals as small as mice. Likewise, human pumps are bulky, battery-operated, and have limited control of dosing. Our FlashSyn pump system is significant in that it provides a **scalable, wirelessly-operated electronic drug infusion system** that will revolutionize drug delivery in a multiple fields of drug delivery, including laboratory animal research, veterinary therapies, and clinical care (Fig. 1).

Figure 1. FlashSyn™ implantable micropump (16 x 12 x 8 mm³, small enough for mouse).

Our **technical innovation** includes: (1) **low power** and **high accuracy** electrolysis-based actuation; (2) **miniaturized form factor** for subcutaneous implantation in mice; (3) **refillability** for chronic studies >12 months; (4) **on-demand, automated electronic control** of dosing and drug profile (e.g. zero-order or sustained); and (5) completely **wireless operation**. Microelectromechanical systems (MEMS) technology allows components to be precisely miniaturized and batch fabricated, moving parts to be minimized, and greater dosing accuracy to be achieved (< 5% error)[17, 18]. Automation improves study outcomes, reduces research costs, and facilitates efficient drug development. Wireless physiological parameters monitoring in laboratory animals[19] reduces stress related to measurement[20, 21] and the use of restraints[22], reduces the number of animals per study[23, 24], and permits 24 hr data collection without artificial animal-human interactions[25]. Wireless drug administration has similar benefits and also enables high throughput administration in multiple animals in separate trials. Drug in the refillable reservoir can be changed, offering additional flexibility and advance experimental design.