B. Significance

B.1 Drug administration: a critical tool in biomedical research and clinical care

A critical capability is the infusion of drugs, toxins, neurotransmitters, and other biochemicals. Reliable chronic administration tools for mice are urgently needed given the wide diversity of drug-induced, transgenic, and knockout mouse models of human disease. In 1996, 21 million rats and mice were used in animal research in the US constituting 91% of all laboratory animals, the majority of which were mice[1]. Many novel drugs, such as biologics, siRNA, peptides, and small molecules, require special dosing regimens[2]. Current administration technologies are insufficient, resulting in inadequate work arounds and potential for missed therapies. Only one in 10,000 drug candidates successfully attains FDA approval[3]. Rapid evaluation of efficacy, safety and toxicity in mice is now possible with our **fully automated, wirelessly-controlled drug dosing system**.

B.2 Few and imperfect administration technologies for research animals

There is a ***longstanding unmet need*** for cost-effective and advanced administration technologies for small animals capable of automated chronic dosing over a wide range of dosing regimens, especially in large scale studies requiring improved workflow, increased productivity, and automation. Manual administration (oral, intravenous, intraperitoneal) requires repeated handling and is most suitable for intermittent dosing[4]. The associated induction of stress ("white coat" effects)[5] may result in undesirable changers in physiologic parameters (concentrations of corticosterone, glucose, growth hormone, or prolactin, heart rate, blood pressure, and behavior)[6, 7]. While chronic dosing is possible using a motor driven infusion pump and catheter tether attached to the body via an implanted port, the tether poses risks of infection and entanglement[8, 9]. Associated abnormal responses include decreased exploratory activity, increased stereotypies, aggression and immobility, and altered stress hormone response[6, 7, 10]. The sensitivity of administration to stress and environmental factors is well documented, motivating naturalistic settings and ambulatory pumps.

Figure 1. Comparison of FluidSync™ pump against the Alzet and Primo pumps.

Few implantable pumps are available for small animals (Fig. 1). The [redacted] osmotic pump [redacted] (Ceq.) provides constant, single flow rate delivery in a compact pill-like package. Drug volume is limited (<1 month) and flow rate cannot be changed. The [redacted] peristaltic pump [redacted] provides some electronic control of drug delivery (limited programmed steps, flow rates, and infusion durations) and is refillable. However, the pump is too large for mice, is always ON (even when drug is not needed), and has only 6-month battery life. Payload and battery limitations necessitate risky surgical replacement of pumps for chronic dosing. Most importantly, the study cannot be ***asynchronized*** for group housing, simultaneous dosing, and batch testing.

B.3 Outcomes improved in animal studies using telemetry

Radiotelemetry used for monitoring physiological parameters in laboratory animals[11] reduces stress related to acquisition of measurements[12, 13] and elimination restraints[14]. Telemetry allows reduction of use of animals[15, 16] and 24-hour data collection without artificial animal/human interactions[17]. Similar benefits in improvement of study outcomes and animal welfare are gained with wireless implantable infusion systems. Automated wireless evaluation of multiple animals allows for higher throughput compared to tethered administration.

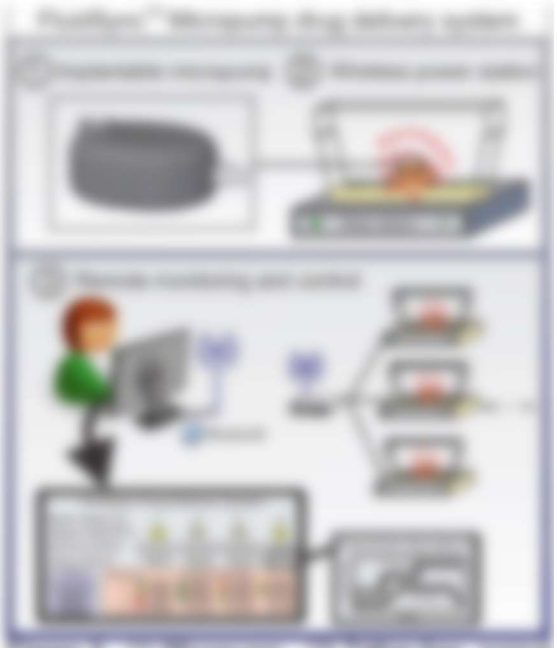

Figure 2. (1) Micropump. (2) Valve that routes behavior anywhere within a cage. Wireless controller under the cage can control multiple pumps in the same cage. (3) User controls dosing (multiple cages if animals) via software interface.

C. Innovation

The FluidSync™ micro infusion pump system is the ***first and only wireless and tether-free administration system*** for mice (Fig. 2). ***Our vision*** is a ***smart vivarium where a network of implanted micropumps are remotely controlled from a single computing station***. End users are animal researchers in academia and industry who need to control external experimental variables and labor costs, minimize infection risks, manage drug toxicity with accurate dosing, reduce repeated implant surgeries, and adjust dosing on-demand to lock in the highly drug regimens over a sustained period.

The specific features that enable our innovative system are: (1) ***low power*** [redacted] and ***high accuracy*** (< [redacted] error)[18-20] electrolytic