A. Specific Aims

The controlled delivery of agents, including emerging biologics, siRNA, peptides, and small molecules, is an important capability in a multitude of clinical and preclinical research applications including neuroscience, pharmacology, toxicology, and physiology. In the pharmaceuticals industry, drug administration in laboratory animal studies is critical in the drug discovery and development process. Administration is predominantly conducted by manual handling and needle injection which is labor-intensive for chronic dosing, but induces stress and other 'white-coat' effects on the animal confounding the experimental results. Alternative technologies for small animals (e.g. tethered external infusion and implantable pumps) are also insufficient. External infusion pumps require a tether which poses infection and catheter entanglement risks. The tether limits natural movement and behavior resulting in abnormal responses such as decreased exploratory activity, increased stereotypies, aggression, immobility, and altered stress hormone response. Commercially available implantable pumps are either too large in size, limited in payload capacity, or limited in infusion capabilities.

To fulfill the unmet need for automated chronic dosing in small animals, we introduce an innovative FluidSync™ implantable drug infusion micropump system that is electronically controlled and allows automated infusion of any liquid formulation regardless of its physicochemical properties. The FluidSync™ micropump will be miniaturized for use in small animals, especially rodents. Mice are the most widely used animal model but drug infusion options are limited. Our pumps are refillable providing a virtually endless drug payload while only requiring a single surgical procedure. Drug dosing can be remotely controlled using an external wireless controller placed below a standard cage that is interfaced to a graphical user interface installed on a personal computer. Pre-programmed dosing regimens or on-demand dosing per user input can be performed. Electronic control and the unique pumping mechanism enable our system to achieve precise dosing over a wide dynamic range of flow rates (nL/min – µL/min) and address any desired regimen, including titration. This new advance will allow users to fully control the initiation, on-demand updates, and conclusion of the dosing regimen. Additionally, this is the first system capable of event-triggered dosing, making possible behavioral studies that have been difficult to implement thus far. Our vision is to realize a smart vivarium. Such a drug delivery platform can benefit investigators from many NIH institutes supporting the biomedical, neuroscience, and behavioral research.

Micropumps and wireless controllers were successfully demonstrated in NIH-sponsored research at the University [redacted] but the research devices were assembled manually one at a time and customized to a specific application. Fluid Synchrony LLC, a university-based startup, was formed to transition these tools from lab-to-marketplace and address demand for these micropump systems by animal researchers from academia, pharmaceuticals industry, and clinical research organizations. Fluid Synchrony received an NSF Phase I SBIR award to establish feasibility of (1) pump component miniaturization, (2) wireless control and operation of a single pump, and (3) benchtop verification of a prototype pump system. This NIH SBIR proposal will advance commercial readiness by demonstrating robust control of multiple pumps simultaneously, *in vivo* verification in multiple mice under vivarium conditions with bioluminescence imaging, and micropump implantation biocompatibility. Three specific aims are proposed:

Specific Aim 1: Develop robust inductive power transfer system for orientation-independent wireless activation of multiple pumps per cage. We will enable robust control of multiple pumps within a cage by integrating an orthogonal three-coil power receiving system within each pump. Building upon a component miniaturization and integration process established during our NSF Phase I SBIR, we will design, integrate and test this novel approach to battery-less activation of multiple pumps within a single cage. We will perform systematic benchtop characterization of circuit components to ensure power transfer in all possible pump orientations, establish and address possible modes of interference, and ensure integration within user-defined pump packaging and size constraints. (Months 1-5)

Specific Aim 2: Demonstration of consistent wirelessly performance of single and multiple pumps. The system consists of the wirelessly operated implantable pump, external wireless controller, and intuitive user interface software. We will demonstrate repeatable and consistent performance (activation and pumping) of pumps anywhere within a mouse-accessible volume of a standard vivarium cage. We will test operation of single and multiple pumps (n=5) (simulating one or more implanted animals) in a single cage. (Month 10-18)

Specific Aim 3: *In vivo* demonstration of group wireless dosing and bioluminescence imaging. Micropumps will be implanted into luciferase-expressing transgenic mice and filled with luciferin. The freely-behaving mice will be group-housed in a single cage, receive intraperitoneal dosing via wirelessly controlled, and verified using *in vivo* bioluminescence imaging. Imaging data from manual injection will be compared to data from pump-infusion in acute and chronic dosing studies. Following the studies, histological tissue analysis will be performed to demonstrate biocompatibility. (Month 19-24)