cage, and simultaneously infused with luciferin via wireless signaling. Analyses will compare *in vivo* bioluminescence imaging following varying modes of administration (needle or pump infusion), luciferin concentration [redacted] mg/mL), and infused volumes [redacted] µL). These studies included on-demand dosing of multiple mice and modulation of delivery rate. The programmable control software will demonstrate automated operation, datalogging, and the ability to create, save and modify dosing schedules. Tissue histology studies will be performed to demonstrate biocompatibility and utility of the micropump for chronic implantation.

Preliminary Results: In a pilot study, one micropump was implanted subcutaneously in a luciferase-expressing transgenic mouse (Fig. 1). The pump was connected to a catheter [redacted]. The micropump was then filled with luciferin (**[redacted]** mg/mL) by percutaneous needle injection into the refill port. The mouse was anesthetized, received IP **[redacted]** µL luciferin via needle, and imaged every 10 min to establish a bioluminescence baseline of magnitude and time course. For four weeks, the mouse was placed above the base station, wirelessly triggered to dose IP **[redacted]** µL luciferin via pump, and imaged. The micropump was successfully implanted for over **[redacted]** days, refilled *in vivo* multiple times, controlled remotely via the base station, infused luciferin on-demand, and induced a measurable bioluminescent signal with a pharmacokinetic profile expected of IP infusion. The peak of bioluminescence was determined to be **[redacted]** hours post-infusion.

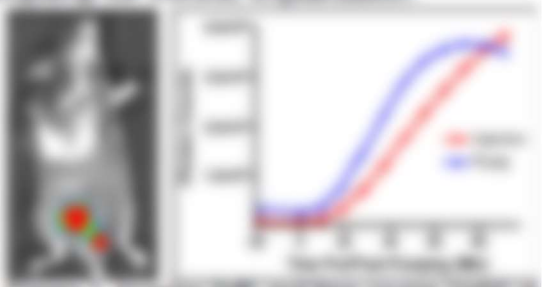

Figure 1. Imaging (left) and time course (right) of bioluminescence following IP infusion of luciferin in luciferase-expressing mouse with pump.

In a second pilot study, two micropumps were implanted subcutaneously into a mouse model of medulloblastoma leptomeningeal malignancy (LM) and connected via catheter to intraventricular (I.V.) cannulas. The LM model was developed by injecting bioluminescent **[redacted]** medulloblastoma cells into the cisterna magna (a region containing CSF under the cerebellum). Mice injected with these cells reproducibly develop LM disease with 100% incidence. These two implanted mice and four non-cannulated nude mice were injected with **[redacted]** cells and allowed to establish tumor growth for 4 days. Pumps were loaded with **[redacted]** µg/ml topotecan, and **[redacted]** µl were pumped I.V. every 3 hours (totaling **[redacted]** µg topotecan per day) during the therapeutic periods. The non-cannulated mice were injected once daily with IP doses of either topotecan at **[redacted]** mg/kg/day (**[redacted]** µg in a 25 g mouse) or an equal volume of saline. This IP dosage was previously found to provide the highest efficacy with the lowest toxicity against subcutaneous tumors in nude mice [1]. Xenogen images of bioluminescent tumors in the CSF for the first 11 days of the study suggests superior inhibition of tumor cell growth in the mice treated with melanoma pump-infused I.V. topotecan (Fig. 2). This is in contrast to the continuous growth of tumors in the IP injected topotecan and saline groups. **[redacted]** Our micropumps enabled this novel melanoma chemotherapy and this study on its efficacy compared to traditional systemic chemotherapy.

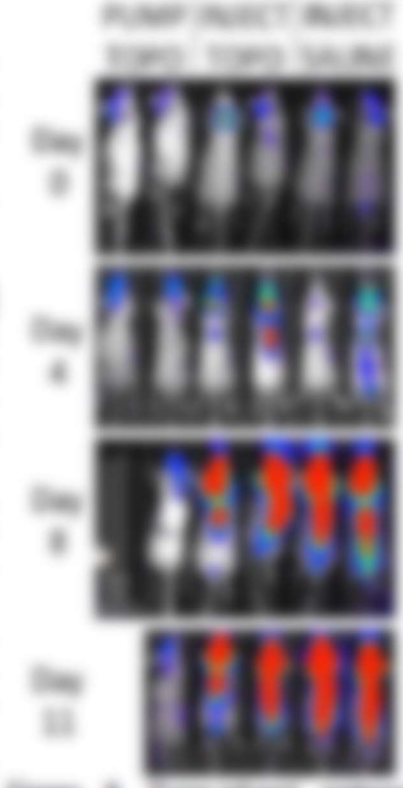

Figure 2. Pump-infused melanoma topotecan (**[redacted]** µg/day) is superior to daily bolus injections of topotecan (**[redacted]** µg/day) or saline, in a mouse model of CSF **[redacted]**

Approach: Micropumps will be subcutaneously implanted in luciferase-expressing transgenic mice (n=5) and connected to catheters **[redacted]**. All pumps will be filled with luciferin (either **[redacted]** mg/mL) using percutaneous needle injection. All implanted animals will be housed in a single cage placed above the base station and freely moving when the software program automates the *in vivo* dosing. In control studies, each mouse will receive a bolus (**[redacted]** µL luciferin) by IP needle injection. Bioluminescence imaging acquisition will be performed at 1.5, 4.5, and 7.5 hours post-injection to establish the baseline magnitude and time course of luciferase activity for each given mouse. Next, an acute administration study will be performed using multiple, short time interval (3 hours) dosing (**[redacted]** µL each) on demand. Again, imaging will be performed at 1.5, 4.5, and 7.5 hours post-infusion. Compared to the imaging control data, data from this acute study will demonstrate repeatability of pumping as well as dosing to maintain stable levels of infused agent at a targeted level (e.g., a therapeutic level). A chronic administration study lasting four weeks will be performed using weekly pump filling, group housing, wireless-controlled dosing of luciferin (**[redacted]** µL), and imaging at 1.5 hours post-infusion to verify simultaneous dosing capability, repeatability, and reliability. With only one