Nanofiber-Based Opioid Bandages for Localized Treatment of Burn Pain

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Statement of Purpose: During recent military operations in Iraq and Afghanistan, thousands of United States military personnel have suffered serious burn wounds. Current thermal and chemical burn care practices, such as debridement and physical therapy, produce intense pain for patients, resulting in several later complications such as chronic pain and peripheral neuropathy. The management of this intense pain relies almost exclusively on systemically administered opioids or other pain medications, which are known to produce side effects as serious as opioid dependence. In order to reduce the total amount of fentanyl required for treatment and alleviate issues with opioid dependence, Luna is developing nanofiber-based dressings that allow controlled loading of fentanyl at very low concentrations, with the ability to tune release profiles and rates. The bandage utilizes significantly less fentanyl than existing Duragesic patches or intramuscular/venous injections, but is demonstrated to provide similar, and potentially localized, therapeutic relief.

Methods: Dressings are produced using pilot scale electrospinning on an Elmarco NanoSpider system. TuneCoat chemistries investigated included GlycoMaxx and PDLLA, with fentanyl and gabapentin drug loading confirmed. Immersion and *ex vivo* dermal release studies were performed, and custom HPLC analysis methods were implemented for monitoring release profiles. Biocompatibility of dressing chemistry was confirmed through standard toxicity, sensitization, irritation, and bacterial reverse mutation studies. A subcutaneous implantation model (rat) was performed to ensure no inflammatory response, with dressings analyzed over 7, 14, 21, and 28 days. A rat model of unilateral hindpaw burn injury was also implemented, with dressings applied daily and von Frey filament mechanical withdrawal threshold determined on days 1, 3, 5, 7, and 14. Stimulation to determine effectiveness of pain relief was performed 18 hours after the dressing change to assess sustained pain relief. Controls included no treatment, intramuscular fentanyl injections, and dressing shams without fentanyl. The withdrawal threshold was determined as a function of the theoretical total drug delivered.

Results: Fentanyl-loaded dressings were produced at pilot scale (square feet per hour) and scanning electron microscopy indicated nanofibrous structure, with negligible change to diameter or morphology when loaded with up to 1.5% (wt/vol) fentanyl. Immersion release studies demonstrated burst or zero-order fentanyl release, depending on dressing chemistry. The total theoretical loading and release rate could be controlled by tuning the total fentanyl loading for each chemistry. Cytotoxicity and genotoxicity tests indicated that the dressings were compatible with L929 cells and demonstrated no genotoxic

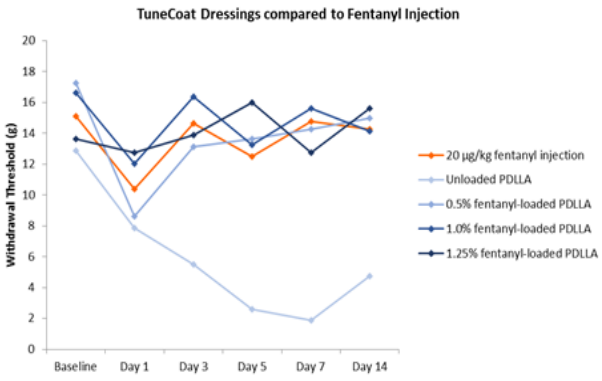

Figure 1. *In vivo* results demonstrate similar responses associated with application of Luna's TuneCoat Dressing as compared to a 20 µg/kg injection of fentanyl.

effects in the bacterial reverse mutation study. Systemic toxicity, pyrogenicity, and skin irritation tests also showed no issues. The subcutaneous implantation model demonstrated no observable inflammation or systemic effects for the entire 28-day study period. The rat model of burn pain clearly showed a dose-dependent effect for fentanyl loading dressings, with demonstrated withdrawal threshold increases (less sensitivity to pain) for fentanyl-loaded TuneCoat dressings as compared to TuneCoat dressing shams (no fentanyl loaded). Rats receiving intramuscular fentanyl delivery of 40-60 µm/kg/day suffered from muscle constriction and breathing difficulties, whereas those treated with fentanyl dressings were mobile and demonstrated no adverse effects. The threshold (grams) for mechanical withdrawal was lower for TuneCoat dressings than IM injection. A single 1-cm^2 dressing was calculated to deliver less than 20% the total amount of fentanyl delivered via injection, yet was demonstrated to produce approximately 75% the total pain relief, with sustained delivery and action at least 18 hours after dressing application.

Conclusions: Luna has demonstrated that nanofiber-based dressings can be produced with varying concentrations of fentanyl. A rat hindpaw burn pain model was utilized to evaluate efficacy of delivery, and significant, dose-responsive pain relief was observed. The chemistry of the dressing was shown to modulate fentanyl release profiles and rates *in vitro*, and these release profiles and rates were directly correlated with *in vivo* pain relief.

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