Photodynamic Therapy System for Prevention and Treatment of UTIs in Neurogenic Bladder

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**Abstract**

Over 3 million people in the U.S. with disease-related (stroke, Parkinson’s, MS, etc.) nerve damage to the bladder must self-catheterize multiple times daily to drain urine. Repeated catheterization results in bladder infections that generate millions of clinic, ER and hospital visits every year with annual medical costs topping $600 million. Current treatment is limited to antibiotic therapy whose chronic use can make the culprit bacteria more drug resistant. We have conceptualized a combination photodynamic therapy (PDT)-catheter system that would enable patients to economically prevent or treat these UTIs at home without specialized medical support or the risk of inducing drug resistance. The PDT drugs proposed are a proprietary combination of generic drugs currently in clinical use and the catheter is a modified Foley capable of channeling a drug-activating light dose into the bladder. The patient would insert the Foley, drain urine, instill PDT solution, activate a built-in light source to activate the drug, and drain PDT solution at the end of treatment. Treatment time would likely be less than one hour. We propose to conduct a proof of concept of therapeutic treatment in a rat model that will facilitate startup company formation for further development of this technology platform.

**Specific Aims and Deliverable (12 Month Project Period)**

**Specific Aim:** Demonstrate that bladder instillation of a methylene blue/potassium iodide photosensitizer solution followed by a drug-activating light dose can disinfect the rat bladder infected with UTI-generating strains of bacteria.  
**Deliverable:** Show ability of a single PDT treatment to safely reduce colony counts of bacteria introduced into the bladder of a rat by at least 7 log.

**Significance**

Nearly 11 million people in the US and over 50 million people worldwide live with neurogenic bladder, a condition under which bladder function is compromised by injury or disease, as a result of another disease. Neurogenic bladder is a common comorbidity in multiple sclerosis, stroke, Parkinson’s, spinal cord injuries and spina bifida. Neurogenic bladder results in urinary incontinence and/or retention due to the absence of nerve signaling for bladder voiding. Patients must self-catheterize (or be catheterized) multiple times daily to void urine. An understandable and unavoidable complication of such chronic catheterization is the development of urinary tract infections (UTIs). Based on current estimates of neurogenic bladder prevalence in a number of key medical conditions (Lansang and Krouscop 2004; Verhoef *et al.* 2005; Manack *et al.* 2011), the number of patients living with neurogenic bladder is likely to exceed 3 million people in the U.S. and 22 million globally.

The frequency of symptomatic UTIs in this population may be as high as 1-2 episodes per year (Hess *et al.* 2008; Singh *et al.* 2011). A healthcare utilization study in 46,271 people living with neurogenic bladder (Manack *et al.* 2011) found that about *one-third* of these patients required medical attention for urinary tract infections over a four-year period. Neurogenic bladder-related UTIs likely generate hundreds of thousands of outpatient visits, ER visits and hospitalizations per year with estimated direct annual medical costs exceeding $600 million. These statistics do not account for the personal misery of these episodes and the inconvenience and costs to the patients in the form of missed work hours and out-of-pocket medical expenses.
Background

The combination of dysfunctional bladder voiding and repeated daily catheterizations makes bacterial colonization of the bladder inevitable and subsequent infections almost unavoidable. Medical intervention typically occurs after symptomatic infection and usually involves therapeutic use of antibiotics (ABs) to eradicate pathogenic bacteria; AB prophylaxis does not appear to impact symptomatic infection rates and can promote drug resistance (Morton et al. 2002). Therapeutic application of ABs for UTIs now takes place in the context of a serious, growing threat of multidrug-resistant bacteria (Picozzi et al. 2014) with repeated AB treatment increasing the likelihood of producing resistant organisms (Hillier et al. 2007). The use of photodynamic therapy (PDT) has been considered as an alternative to ABs, and many in vitro studies have been conducted (Wainright et al. 2010). However, PDT traditionally requires skilled medical technicians to administer the drug and treat the patient, uses expensive, proprietary photosensitizers that may not represent an attractive economic cost-benefit analysis and may require a prolonged incubation before photoactivation. Not surprisingly, this approach has not been aggressively pursued for treatment of bladder UTIs.

Over the last two years, a team from the Department of Medicine has worked collaboratively with investigators from both the Urology and the Wellman Center for Photomedicine to create a better, more economical approach that could be used by patients themselves to both treat and prevent such UTIs. Dr. Michael Hamblin of the Wellman Center has identified a synergistic combination of two existing generic drugs with PDT potential—methylene blue (MB) and potassium iodide (KI)—that together yield a 1000-fold improvement in bacterial killing compared to either drug alone. Both drugs have been used clinically in bladder diagnostic procedures and are relatively safe and tolerable. An MB + KI solution could readily be delivered to the bladder through existing catheters. Unlike with typical PDT treatments, light activation of the photosensitizer could begin shortly after its introduction into the bladder. Since bacteria bind dye rapidly while host cells take up dye slowly, this approach would maximize selectivity for bacteria over host cells. Shortly after instillation, a fiber optic cable with diffuser attached to a low-power red light source (~660 nm) inside a urinary catheter could deliver a drug-activating light dose. The light dose causes electron transfer from the excited state of MB to KI, producing iodide radicals that can kill bacteria. Since PDT killing of bacteria uses a fundamental mechanism of photochemical damage to cell wall constituent molecules, it is unlikely that bacteria will develop resistance to this bactericidal mechanism, making its chronic use possible and reducing the likelihood of drug-resistance.

The Medicine team worked with both Urology and Wellman to design a catheter to simplify treatment delivery. The resultant “Photonic Foley” incorporates a fiber optic cable into a standard Foley to enable diffusion of light from an externally connected light source (Figure 1). It features a port to drain urine and instill photosensitizer and one to introduce intralipid into the inflatable balloon of the catheter as a light diffuser. The catheter requires minimal redesign, lowering development costs. The relative simplicity of the proposed treatment approach—drain urine, instill photosensitizer, turn on light, drain photosensitizer—means bladder disinfection could be performed by nursing or paramedical staff or patients themselves. The components could make a commercial treatment economical for the neurogenic bladder market. The drugs are relatively inexpensive, current Foley catheters cost below $10 each and light treatment requires a low-power, visible light source that could be provided by an inexpensive LED system.

Preliminary Results

The Hamblin laboratory has shown that in vitro the addition of a harmless solution of KI (10 mM) to the photosensitizer solution (200 µM MB) followed by illumination with extremely low fluences of red light leads to killing of the Gram-negative uropathogenic bacterium E. coli (UPEC) at 3 logs more (1000 times greater) efficacy than MB alone. In addition, his laboratory successfully established two transgenic models of luciferase-
expressing bacteria—*Escherichia coli* and *Proteus mirabilis*—to allow the monitoring of bacterial viability in real time. A Photonic Foley catheter prototype has not yet been constructed, but the German catheter company Rüsch produced a similar prototype for PDT of bladder cancer (Eichenauer *et al.* 1998), suggesting this approach is feasible.

**Approach**

For the proposed study, the team would re-establish the photoluminescent bacterial strains developed by Dr. Hamblin for such bladder studies. We will establish that these are capable of successful chronic colonization of a Sprague-Dawley rat bladder and conduct studies to demonstrate that light emission readings are consistent with actual colony counts. We will establish a technique for bladder instillation of the luminescent bacteria and the photosensitizer drug in female Sprague-Dawley rats similar to that used in instillation of bladder cancer cells and intravesicular drugs in the same rat model (e.g., Gomes-Giacoia *et al.* 2014). Typically rats will be anesthetized and urethras cannulated with a 22 gauge Teflon angiocatheter. Urine will be drained and then approximately 200 µl of either a PBS solution containing up to MB+KI solution instilled. Typical bacterial doses are $3 \times 10^6$ CFU for urinary pathogenic *E. coli* and $1 \times 10^5$ for *P. mirabilis*. For therapeutic treatment, we would subsequently insert a 100 micron optical fiber with a diffuser at the end of a 660 nm light source to illuminate the bladder.

Following the establishment of the rat colonization and catheterization studies, we will perform a treatment study to show that introduction of a physiologically-appropriate photosensitizer dose for a relatively short period of time (less than 10 minutes), followed by treatment with red light for varying periods of time introduces a log-linear bacterial killing curve similar to that seen in the *in vitro* studies of Figure 2. We will then perform a study to show that treatment at the predicted dose of light can produce effective eradication of the bacteria ($7+ \text{ log killing}$) with one treatment. Following the extinguishing of a bacterial signal, rats will be euthanized and bladders removed to culture for remaining bacteria and to examine for any evidence of tissue damage.

**Timeline and Milestones**

Quarter 1: Establish rat model of bacterial bladder infection  
Quarter 2: Conduct pilot dose-response studies  
Milestone: PDT studies show 7 log or greater reduction in bacterial load after single PDT treatment.

**Budget**

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<td>Sprague-Dawley rat purchase (72 at $60 with shipping)</td>
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**Next Steps**

The Innovation Fund monies will be used to generate positive data from the proof of concept study that will help us raise an initial equity investment around a startup seeded out of MGH. We have interested investors but the initial POC is lacking.
References


