



## Emergence of a spinal micturition reflex after SCI: abolition by silencing of hyperexcited C-fiber bladder afferents by gene therapy to restore continence and micturition, (ELPIS)

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This program aims to develop a gene therapy to treat neurogenic detrusor overactivity (NDO) and ultimately to restore urinary continence and voluntary micturition, which remains an unmet medical need in spinal cord injured patients who are currently emptying their bladder by intermittent catheterization. NDO is a severe disabling disorder caused by spinal cord injury (SCI) and characterized by involuntary bladder contractions, resulting in urinary incontinence, recurrent urinary infections and, if untreated, renal failure, which can be fatal. The role of the bladder is to store urine excreted by the kidneys. When the bladder is full, micturition occurs consisting in bladder emptying by contraction of the bladder muscle and opening of the urethral sphincter. Bladder function is controlled by a reflex organized as a neural loop, constituted of nerves from the bladder to the spinal cord (bladder afferents) and back from the spinal cord to the bladder (bladder efferents) and the urethral sphincter, with the spinal cord being under the control of the brain. After SCI, bladder afferents send aberrant information to the spinal cord resulting in chaotic bladder contractions. There is also a loss of brain control on the spinal cord responsible for a lack of voluntary control on micturition. Current NDO treatments comprise oral antimuscarinics or botulinum toxin (BoNT) injections into the bladder, both of which inhibit bladder contractions by blocking bladder efferents, consequently paralyzing the bladder. Intermittent bladder catheterization (5-6 times a day) is therefore mandatory for bladder emptying, which is responsible for recurrent urinary infections and for a significant decrease in quality of life by increasing disability. We aim to design an original gene therapy to inhibit the transmission of aberrant information from the bladder to the spinal cord via bladder afferents to treat NDO without bladder paralysis. We will design herpes simplex virus-based vectors to be injected into the bladder to silence bladder afferents neurons. By infecting bladder afferents, these vectors, will blunt their intracellular machinery for neurotransmission by expressing relevant intracellular transgenes. Vectors will be tested and selected in a variety of assays, including SCI rats with NDO to assess their therapeutic effect and safety. The neural command of micturition will thus remain available for on-demand electrical stimulation by an implantable stimulator (already available in humans) to elicit micturition without bladder catheterization. Ultimately, this should revolutionize the management of NDO in SCI patients.