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R11: A NOVEL CELL PERMEABLE PEPTIDE WITH RAPID AND PERSISTENT BLADDER UPTAKE ALLOWING INTRAVESICAL INSTILLATION THERAPY

Hypothesis / aims of study

Cell permeable peptides (CPPs) are short cationic peptides that can cross the plasma membrane efficiently and result in a rapid uptake by mammalian cells in vitro and in vivo (ref.1). We have shown that, in genitor-urinary organs, a polyarginine-R11 is the most efficient CPP over several other synthetic CPPs (TAT, PENE, KALA and K11) (ref 2). However, the glycosaminoglycan layer may represent an impassable barrier for R-11. With drug delivery in mind, we tested the uptake efficiency of R11 administered intra-vesically with recovery after 3 hours and 24 hours.

Study design, materials and methods

An in vivo model (athymic nude mouse) approved by Institution Animal Care and Usage Committee was employed. Synthetic R11 labelled with fluorescein isothiocyanate (FITC) was tested at the concentrations of 1 □M and 5 □M. Controls received FITC without CPP conjugation. All animals were instilled with R11 for 30 minutes and sacrificed 3 hours and 24 hours later to harvest their bladder for the measurement of CPP uptake and tissue localization using OCT frozen section. Bladder uptake specificity was determined by averaging relative FITC intensity with each tissue weight; these data were then compared with other major organs.

Results

As shown in the histogram, although the uptake of R11 varied among animals, a 2 to 6 fold higher amount of R11 was detected in the bladder after 3 hours (Fig. B) and 24 hours after intra-vesical instillation at 1□M or 5 □M concentrations (Fig.A) over the detection rate in each animal control group (n=4) or other organs. Compared to controls, tissue sections (x 40) further confirmed the localization of R11 in the lamina propria of the bladder wall (Figure C).

Figure A

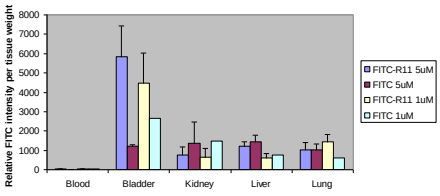
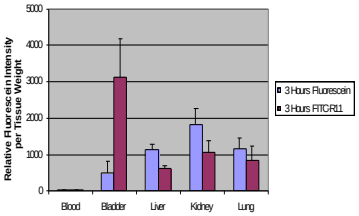


Figure B



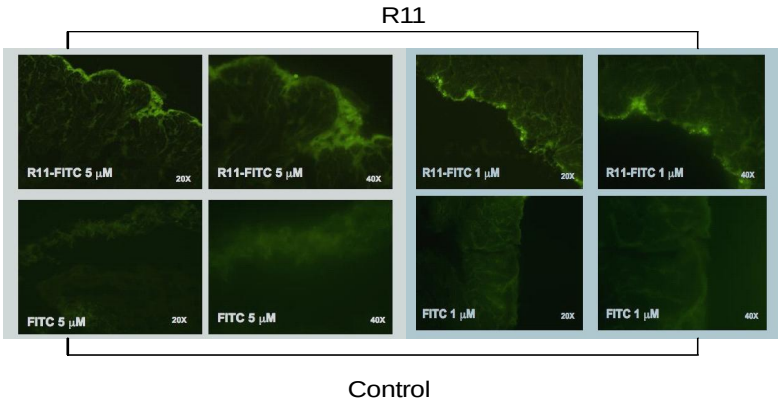


Figure C

Interpretation of results

Uptake of R11 in the urothelium after intravesical instillation was noted after a long and a short recovery time at two different concentrations, indicating a rapid uptake and a durable persistence in the bladder wall. This finding suggests a potential for treatment effectiveness when R11 will be coupled with pharmacologic agents for treatment of bladder conditions like bacterial or interstitial cystitis.

Concluding message

Because of its high affinity for bladder, both systemically in prior studies (ref.2) and after intra-vesical instillation as reported herein, R11 can be further tested in this animal model as a delivery vector for therapeutic agents in bladder diseases.

References

1. Science 1999, 285:1569
2. Cancer Res. 2006, 66:8954

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Is this a clinical trial?	**No**
What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**Institution Animal Care and Usage Committee**