Universität Basel

Research Project

Antagonists of Type 1 Fimbriae-mediated Adhesion of Escherichia coli: Treatment of Urinary Tract Infections

Third-party funded project

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Urinary tract infection (UTI) is an inflammatory, pathogen-caused disease that occurs in any part of the urinary tract. UTIs are among the most prevalent infectious diseases in general and of any organ system. Its magnitude can be estimated in the United States by the number of visits to physicians (about 8 million/year) or hospital discharge diagnoses (about 1.5 million/year). Particularly affected are women, who have a 40%-50% risk to experience a symptomatic UTI at some time during their lifetime; more than half of them will experience another infection within 6 months.

All symptomatic UTIs should be treated with antibiotics to prevent potential devastating complications. However, recurrent infections with subsequent antibiotic exposure can lead to emergence of antimicrobial resistance, which often leads to treatment failure and reduces the range of therapeutic options.

Hence, it is an urgent need of public health to develop an efficient, cost-effective and safe non-antibiotic therapy to both prevent and treat UTIs without facilitating antimicrobial resistance. Inhibition of type 1 fimbriae-mediated bacterial attachment to the bladder epithelium is a very promising approach to achieve this aim.

Our goal is to identify FimH antagonists with properties required for a therapeutic application. However, carbohydrates exhibit two inherent drawbacks in respect to their therapeutic potential; they generally show only modest affinities to their targets and, in addition, they do not fulfill even basic requirements in respect to their pharmacokinetic properties, especially their high polarity does not allow an oral application.

Our search for FimH antagonists covers various research areas, namely chemistry, pharmacology, microbiology and medicine. Therefore, we propose an interdisciplinary project organization reaching from antagonist design and synthesis to the biological evaluation in *in vivo* models. The main expertise is available within the labs of the applicants. Additional support will be gained by external collaborations.

The starting point are FimH antagonists recently identified in our lab. Besides high affinity, the compounds exhibit promising pharmacokinetic properties. Based on the crystal structure of FimH, a second generation of antagonists will be designed and synthesized. For the biological evaluation, a flow chart

containing *in vitro* affinity assays, assays for the determination of PK properties, cell assays and *in vivo* disease models will be established.

The overall goal of the project is to develop a prototype of a FimH antagonist, which fulfills pharmacodynamic as well as the pharmacokinetic requirements for a successful UTI treatment. A major challenge will be the design of an orally available and therefore lipophilic FimH antagonist, which is not systemically metabolized, but unchanged renally secreted to bind with high affinity to type 1 fimbriae of *E. coli*.

Keywords Escherichia coli, urinary tract infection, fimbriae-mediated bacterial adhesion, mannosides, pharmacokinetic properties
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