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An “omics” approach to uropathogenic *Escherichia coli* vaccinology

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Urinary tract infection (UTI) occurs when bacteria, most commonly uropathogenic *Escherichia coli* (UPEC) [1], contaminate the periurethral area and traverse the urethra to colonize the bladder. Left untreated, UPEC ascend the ureters and establish a secondary infection in the kidney parenchyma. At this juncture, UPEC can elicit serious complications including renal scarring, septicemia, and even death. While young women are the most affected population, children, elderly, and hospitalized individuals are also at high risk. Up to 30% of patients experience recurrent episodes, contributing to billions of dollars spent annually to treat these infections [2]. Given the paucity of recent vaccine developments, the increasing rate of UPEC antibiotic resistance, and the need to reduce healthcare expenditures, new avenues of UTI vaccine research need to be explored.

Conventional vaccinology approaches targeting *bona fide* virulence factors, namely FimH of type I fimbriae, have generated promising data in animal models [3] yet no vaccine is currently available in the United States. In Europe, licensed treatments consist of a complex mixture of whole killed bacteria; however, clinical data from the United States regarding recurrence and specific antibody titers does not suggest lasting immunity has been generated by this regimen [4]. Despite the advances afforded by reverse vaccinology (an *in silico* genomics-based approach to vaccine development [5]), it is not practical for UPEC due to a lack of high-throughput methods to test for protection. A more optimal approach to UPEC vaccine discovery would be one that is broad and unbiased yet has some aspect of selectivity to narrow the list of candidates. An example of this has been employed in pneumococcal vaccinology [6]. Applied to UPEC, it might be useful to target only *PASivE* candidates, UPEC proteins that are Pathogen-specific, Antigenic, Surface-exposed, and *in vivo* Expressed. These particular traits are attractive because they ensure that the targets are not widely expressed by commensal *E. coli*, are accessible to and recognized by the host immune system, and are synthesized specifically *in vivo* and likely important for infection and pathogenesis.

To distinguish *PASivE* UPEC proteins, we can collectively analyze the results of genomic, proteomic, and metabolomic screens that each individually implicates proteins with one or more *PASivE* qualities (Table 1). The utility of large-scale genomic screens in bacterial pathogenesis and vaccine research has already been described [5]. *In silico* analyses, similar to those performed in reverse vaccinology studies, can also limit the candidate pool by predicting surface-exposed proteins, potential targets for secreted antibodies. While each

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screen has disadvantages, together they provide a comprehensive and impartial way to determine genes that encode *PASivE* proteins. Thus, screening for these specific candidates enriches for antigens that might provide protection based on biological relevance and creates a manageable number of genes to clone, express, and test in the murine model of ascending UTI.

The results generated by published and ongoing screens are particularly striking. Most of the screens primarily identified different classes of iron acquisition receptors. These outer membrane proteins are responsible for uptake of distinct siderophores or heme and are now *PASivE* candidates suitable for vaccine trials. This result supports the notion that similar to many other organisms, iron is crucial for UPEC to survive in its respective host niche, and the genomic dedication to functional redundancy supports the fact that the mammalian urinary tract is iron-limited. Indeed, mice vaccinated with the denatured IroN siderophore receptor are protected from transurethral UPEC challenge [7], a proof-of-concept for testing other *PASivE* proteins indicated by "omics" screens. Other potential targets identified by these studies include an array of metabolic transporters, putative adhesins, and hypothetical proteins that may represent novel virulence factors.

The testing phase presents a new challenge for UPEC vaccinology. The field should advance towards a subunit vaccine directed against *PASivE* proteins. Additionally, being a mucosal pathogen, the vaccine must be administered with an appropriate adjuvant by a route and schedule that stimulates long-term immunity and not tolerance against UPEC. To this end, animal trials must be used to address these issues and also distinguish immunological correlates of protection and details regarding the molecular and cellular factors that play a role in the adaptive immune response to UTI.

Screening for *PASivE* candidates requires the pathogen be culturable and have an animal model of infection, is limited to the identification of protein antigens, and is benefited greatly by a sequenced and annotated genome. Moreover, while lacking the breadth of coverage and total objectivity of reverse vaccinology, an "omics"-based screening initiative for *PASivE* proteins is particularly useful to produce a list of probable vaccine candidates. This scheme represents a rational approach for vaccine design to curb the social, economic, and personal burden caused by UPEC-mediated UTI. This approach can easily be translated to identify vaccine candidates for other significant human pathogens which are known to cause mucosal and systemic disease.

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Table 1

Screens that can be used to identity PASivE UPEC vaccine candidates.

Criteria	Screen(s)	Reference
Pathogen-specific	Comparative genomic hybridization (CGH)	[8]
	In silico comparative genomics	[9]
	Southern blot	[10]
Antigenic	Two-dimensional SDS-PAGE and Western blot	[10]
	In vivo-induced antigen technology (IVIAT)	(P. Vigil *et al*., unpublished observations)
Surface-exposed	*In silico* mining for genes containing predicted outer membrane protein signatures (transmembrane domains, signal peptide cleavage sites, etc.)	(D. Rasko, unpublished observations)
	Identification of surface peptides by limited proteolysis and tandem mass spectrometry	[11]
in vivo Expressed	Gene expression microarray	[12]
	Two-dimensional fluorescence difference gel electrophoresis (2D-DIGE)	[13]
	IVIAT	(P. Vigil *et al*., unpublished observations)
	Recombinant *in vivo* expression technology (RIVET)	(M. Walters, unpublished observations)
	Quantitative metabolomics	[14]
	Signature-tagged mutagenesis (STM)	[15]