

## Allergy Peptide Array

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This proposal describes the application of a bead-based microarray platform for the rapid and simultaneous screening of multiple allergies. With increasing costs of medical care, rapid tests, which allow multiplexed screening of disease conditions in many samples simultaneously, will be invaluable. Allergies will be screened using the same basic immunoassay format currently employed in allergy testing. The innovation lies in adapting existing solid-phase immunoassay methods to the Sentrix/Tm BeadArray/Tm platform and in multiplexing and miniaturizing the assays. In the R21 Phase, using peanut allergy as a model system for proof of concept, peptide microarrays will be developed for screening peanut allergen-specific IgE binding, using known peanut allergen peptide epitopes. The peptide microarray development will avail of the available ability to synthesize large numbers of different peptides in a short time. Chemistry techniques for conjugating peptides with paired encoding oligonucleotides to beads have been deduced and will be further optimized. The plan for the R33 Phase of this project is to develop methodology on the Sentrix platform to screen multiple food allergies at the same time, including cow's milk, peanut, egg white and soy. Optimization of the multiplexed food allergies will be done to ensure quantitative assays with high reproducibility, precision and accuracy.

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## Transgenic Indicator Cells for Influenza Virus

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Influenza virus causes a pandemic disease of the respiratory tract that results in significant human morbidity and mortality. Diagnosis of influenza virus infection during the winter months makes up a large component of the clinical virology workload. The goal of this application is to develop transgenic cell lines that facilitate the detection of influenza virus (IV) in clinical specimens. Apath has developed and patented methods for detecting

and quantitating other RNA viruses such as Sindbis virus, a positive-strand RNA virus and respiratory syncytial virus (RSV), a negative-strand RNA virus. The RSV system, while very useful as a research tool, is too complicated in its present format to be useful in a diagnostic test for clinical virology laboratories. Recently, they have started developing an influenza virus detection system. They constructed a plasmid in which a polymerase I promoter drives transcription of an influenza A virus artificial genomic RNA segment that carries a firefly luciferase gene. They have found that infection of cells transfected with this eDNA exhibited a high level of luciferase whereas uninfected cells expressed background levels. Apath plans to build on this result and make equivalent influenza B artificial genomic RNA. They will then use these constructs to generate stable cell lines that express a reporter gene only in response to influenza A and/or influenza B virus infection. Such cell lines will form the basis of an influenza detection test which will be developed in Phase II in collaboration with Diagnostic Hybrids, Inc. (Athens, OH) and modeled after an existing FDA approved test for herpes simplex virus (ELVIS(r)-HSV).

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## An In Situ Gelling Nasal Vaccine Delivery Platform

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The nasal cavity represents an easily accessible and effective route of vaccination by which not only systemic, but also mucosal immunity, can be induced. The overall goal is to develop a simple and broad nasal vaccine delivery platform that prolongs the antigen residence time, enhances immune response, and is suitable for many different types of antigens. This platform, trademarked as GelVac, is based on a unique high molecular weight acidic polysaccharide (GelSite™ polymer). The GelSite polymer is capable of gelling *in situ*, changing from liquid to a gel upon contact with nasal fluids, thereby providing a controlled release of the antigen. Preliminary studies have shown a proof-of-concept for the GelVac by demonstrating *in situ* gelling in the nasal cavity and increased serum IgG and lung IgA immune response against a model antigen (DT-CRM, diphtheria toxin mutant CRM) following intranasal delivery.

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## Human Antibodies for Exposure/Protection from Anthrax

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Avanir Pharmaceuticals Inc., has developed a powerful platform for the rapid generation of high affinity fully human monoclonal antibodies that can be selected on their ability to neutralize anthrax toxin PA as exemplified by our lead candidate 8C1 (Kd 1.2 x10<sup>-12</sup>M, KinExA). Here Avanir proposes to continue the development of 8C1 as well as to isolate and characterize additional totally human monoclonal antibodies (MAbs) against *B. anthracis* exotoxin components protective antigen (PA) and lethal factor (LF). Avanir will evaluate and characterize MAbs for affinity (using BiaCore and KinExA) and toxin neutralization (using an *in vitro* cell-based assay). Selected candidates will be further evaluated in a rodent animal model, using bolus challenge with recombinant anthrax toxins. By using multiple human donors, Avanir will access a diverse panel of antibodies and determine the optimal candidate(s) or combination of antibodies required to neutralize anthrax exotoxin *in vivo*. At the completion of this proposed study Avanir will have candidates ready to enter the next stage of animal model evaluation. Testing candidates in live animal models with exposure to aerosolized anthrax spores are beyond the scope/budget of this study and would be the logical entry point for a phase II application. The following Specific Aims will be performed: 1) Generate a panel of high affinity fully human antibodies to PA and LF components of the tripartite *B. anthracis* exotoxin. 2) Evaluate and characterize MAbs binding and efficacy in an *in vitro* protection assay. 3) Determine protective efficacy in a rodent animal model, using bolus challenge with recombinant anthrax toxins.

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## Identification of *E. coli* Anti-Infective rRNA Targets

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Although antibiotics are widely available and effective, infectious diseases caused by bacteria are responsible for millions of deaths each year. Much of this mortality is due to the increasing rise of antibiotic-resistant bacteria easily spread in hospitals and institutions. The emergence of resistant organisms has created a need for new anti-infectives that are less susceptible to antimicrobial resistance. One of the mechanisms used by bacteria to overcome the effectiveness of antibiotics is mutation of the drug target, commonly the rRNA of the ribosome. The overall goal of this project is to develop new anti-infectives by identifying new ribosomal drug targets and all viable mutations of these targets, and using these targets for drug screening. A high-throughput genetic system developed in *E. coli* can be used for identification of rRNA mutations that do not impair ribosome function. The specific aims of Phase I are 1) construction of a functional *E. coli* 16S rRNA mutation library; 2) isolation and sequencing of 5000 mutants; and 3) identification of new drug targets by assaying each mutant for function *in vivo*. In Phase II, new targets and all viable mutations of these targets will be identified and used to screen for new drug leads.

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