Vaccination and antibody: prevention and therapy of nosocomial infections

“Les Pensières”
Fondation Mérieux Conference Centre
Veyrier-du-Lac - France

September 26-28, 2011

Steering Committee:

- Thierry Calandra
- Catherine Dutel
- Jean-Marc Ghigo
- Jacques Louis
- Gerald Pier
- Bachra Rokbi

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Dear Participant,

It is our pleasure to welcome you to the symposium entitled:

‘Vaccination and antibody: prevention and therapy of nosocomial infections’

in Fondation Mérieux’s Conference Center “Les Pensières.” We hope you will enjoy this meeting, which brings together some of the world’s foremost experts.

The format of the discussion is intended to generate discussion and interaction among participants and to foster the dissemination of new information on this topic. The conference will provide an opportunity for specialists to exchange their knowledge and experience through collaboration with researchers from around the world.

Over the next three days, the team at Les Pensières will be on hand to help you with any questions you may have and to make your stay and conference as comfortable and valuable as possible.

Benoît Miribel
Director General
Fondation Mérieux

For more information: [www.fondation-merieux.org](http://www.fondation-merieux.org)
Background and rationale

Nosocomial infections are widely prevalent and account for a substantial increase in morbidity and mortality among hospitalized patients. In addition, bacteria and fungi that are resistant or poorly responsive to multiple antibiotics or antifungal agents often cause these infections.

Although vaccines are firmly established in the public health field as an effective means of preventing infection, attention on the potential role of vaccine and immunotherapy for the prevention/amelioration of nosocomial infection is quite recent especially for those that occur in the critically ill patient.

This meeting will focus on current knowledge about vaccines and immunotherapy for nosocomial infections. Host immunology, as well as lessons learned from vaccines already in use and those under development will be discussed.
### Scientific Programme

#### Monday 26 September 2011

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#### Tuesday 27 September 2011

**Session 1**

**Promises and pitfalls of vaccines for nosocomial infections**

Chaired by Johana Golbergh & Arturo Casadevall

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**Gram negative bacterial pathogens: the more untreatable they become the more we need immunotherapeutic options**  
Chaired by Bachra Rokbi & Gerald Pier

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**Session 4**  
**Gram positive bacterial pathogens: they just won’t go away**  
Chaired by Gregory Priebe

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#### Session 5
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**Targeting viral and fungal nosocomial pathogens for vaccination**  
Chaired by Michael Otto

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Keynote lecture

The epidemiologic, immunologic and microbiologic challenges for vaccines against nosocomial pathogens
The epidemiologic, immunologic and microbiologic challenges for vaccines against nosocomial pathogens

Gerald PIER
Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School - USA

In 1953 Time Magazine quoted no less an authority than Nobel-Prize (1960) winning immunologist Sir MacFarlane Burnet that “It is not too much to say that at the present time no acute infection occurring in a previously healthy individual will result in his death if he reaches a well-equipped hospital before irreparable damage has been done to his tissues. (The only common exceptions: yellow fever and smallpox, which vaccines can prevent).” Now, of course, nosocomial infections in both previously healthy individuals and those with underlying disease represent one of the major challenges in health care, with antibiotic resistant organisms presenting the biggest challenge. A clear improvement in this situation would result from development of vaccines and passive therapies that could confer sufficient immunity in at-risk individuals to stave off the serious consequences of infection. Among the top 10 nosocomial pathogens, accounting for 84% of all hospital-acquired infections, vaccines are technically feasible but progress is primarily hampered by lack of sufficient knowledge of what the optimal immune effectors would be for any given pathogen, the likely high level of serologic variability among targets such as capsules and LPS O antigens, the need for both humoral and cellular effectors such as TH17 cells, and the lack of any framework for immunizing at risk populations prior to the time they enter a hospital. Passive antibody therapies could address some of these but likely a large array of different ones would be needed which could be prohibitively costly. Finally, underlying host immunocompromise often predisposes to nosocomial infection, and such a state can render even the most robust immune effectors unable to provide effective immunity.

One notable antigen that might provide an inroad to some solutions is a broadly-distributed cell surface polysaccharide, a β-1-6-linked polymer of N-acetyl glucosamine (PNAG). Initially described in coagulase-negative staphylococci, PNAG is now known to be expressed by Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, and others.
Suite

Recent work in our group has shown PNAG expression extends beyond prokaryotes to some important eukaryotic pathogens. Most humans have high titers of natural antibody to PNAG but it does not fix complement onto the bacterial surface and hence is not protective. Using a variant glycoform of PNAG wherein most of the N-acetyl groups are removed, synthetic oligosaccharides comprised of nonameric β-1-6-linked glucosamine, or a fully human monoclonal antibody to these forms we have obtained high levels of in vitro killing and in vivo protection against a range of nosocomial pathogens. Among the top nosocomial pathogens, only P. aeruginosa does not produce PNAG. This molecule represents a potential high value target for addressing the major issues associated with hospital-acquired infections and the MAb is in phase II clinical trials in at-risk patients for pharmacokinetics and safety and hopefully will rapidly progress to efficacy studies in the near future.

1http://www.time.com/time/magazine/article/0,9171,822914,00.html?i=xz1Wut1XUYq
Session 1

Promises and pitfalls of vaccines for nosocomial infections
Overview of the problem of nosocomial infections: What are the unmet needs?

Jean CHASTRE
Institut de Cardiologie, Hôpital de la Pitié–Salpêtrière, Assistance Publique–Hôpitaux de Paris, Université Pierre et Marie Curie France

The emergence of antimicrobial resistance in many bacterial species has increased the burden of nosocomial infections. Within the healthcare setting, the unique nature of the intensive care unit (ICU) environment makes it a focus for the emergence and spread of many antimicrobial-resistant pathogens. Patients in the ICU are commonly exposed to broad-spectrum antimicrobial agents, and the ICU presents ample opportunities for the cross-transmission of resistant bacteria from patient to patient. As a result, rates of colonisation and infection with antimicrobial-resistant pathogens are almost always higher among patients in the ICU than in other healthcare settings, either in or out of the hospital. Findings from all epidemiological studies show a steady increase in antimicrobial resistance in P. aeruginosa and other Gram-negative bacilli from ICU isolates, with rates in 2003 of 20% to carbapenems and approximately 30% to third-generation cephalosporins and quinolones. Resistance patterns to antimicrobial agents of Gram-positive pathogens have also changed dramatically during the last decade, with an increasing prevalence of infections caused by methicillin-resistant Staphylococcus aureus (MRSA), methicillin-resistant coagulase-negative S. aureus, and vancomycin-resistant enterococci. Those infections caused by multidrug-resistant strains are often extremely difficult to treat, with mortality in excess of that caused by the underlying disease. Thus, they impose an enormous threat to personal and public health, considerably increasing costs in terms of reduced livelihoods, lost lives, and increased healthcare expenditures. To reduce mortality, the causative pathogen must be eliminated as soon as possible, before the patient's health status becomes irreversible. Furthermore, as long as the patient continues to receive inappropriate antimicrobial therapy, that patient remains a reservoir for a resistant pathogen or pathogens that can spread within the healthcare setting. Extreme care must therefore be exercised when selecting an antimicrobial agent(s) for treatment of infection or suspected infection, employing broad-spectrum empirical coverage when the patient is at risk of infection caused by an antibiotic-resistant pathogen and targeted, narrow-spectrum agents for de-escalation once culture evidence is available or when the local ecology and patient characteristics suggest this approach to be adequate.
Unfortunately, the high level of bacterial resistance observed in patients who develop nosocomial infections limits the treatment options available to clinicians and encourages the use of antibiotic regimens combining several broad-spectrum drugs, even if the pretest probability of the disease is low, because initial inappropriate antimicrobial therapy has been linked to poor prognosis. Besides its economic impact, this practice of «spiralling empiricism» increasingly leads to the unnecessary administration of antibiotics in many ICU patients without true infection, paradoxically resulting in the emergence of infections caused by more antibiotic-resistant microorganisms that are in turn associated with increased rates of patient mortality and morbidity.
Are vaccines a good option for preventing infections in hospitalized patients? Can we intervene more effectively with proper infection control and safety measures?

Susan Huang
Division of Infectious Diseases and Health Policy Research Institute
University of California Irvine School of Medicine - USA

Although vaccines are highly effective for community-based disease, important changes to vaccine implementation models are needed for application to healthcare-associated infections. In comparison to hospital-based infection control measures to prevent nosocomial disease transmission, vaccines are not considered a natural first line defense. Replacements for current infection control measures need to be uniformly effective for all hosts and widely accepted by the public and health care providers. Speed of effect is another barrier for the use of vaccines to prevent healthcare transmission of infectious diseases. Beyond efficacy, important changes to proof of concept and marketing activities are essential to yield highly effective vaccines for prevention of infections in hospitals and long term care facilities. While not insurmountable, critical conceptual changes are essential for successful application of vaccines to the point-of-care medical arena.
The importance of hospital-acquired, community onset infections as targets for vaccination

Scott K. FRIDKIN
Division of Healthcare Quality Promotion, National Center for Zoonotic and Emerging Infectious Diseases, Centers for Disease Control and Prevention - USA

Effective vaccine for common pathogens causing hospital-associated infections could substantially reduce morbidity and mortality resulting from these infections, including S. aureus disease, Clostridium difficile, Pseudomonas aeruginosa, and Candida spp. In the United States, as healthcare delivery continues to change, shifting high acuity of care outside of short-stay acute care hospitals, patients continue to be at risk for infections after discharge from these traditional care settings. As candidate vaccines and the optimal implementation strategies to maximize their public health impact are evaluated, considerations to patients seeking healthcare in a broad variety of settings should be included.

Dedicated surveillance systems to measure incidence of specific types of Healthcare-associated infections for specific pathogens in the U.S. is limited, but includes S. aureus and C. difficile. We have learned that most invasive infections for MRSA, occur within the first few days of hospital admission among persons with obvious healthcare exposures (about 60%); more than during hospitalization (25%). In extrapolating from the 2008 MRSA-specific estimates in the United States, an estimated 163,000 persons developed invasive S. aureus infections with an associated 27,000 deaths; about half of these infections occurred within 4-8 weeks after discharge from a short-stay acute care hospitalization. These earlier hospitalization can be considered possible opportunities for vaccination. Although more traditional population-specific vaccination targets must be considered (e.g., hemodialysis, surgical patients, particularly those undergoing cardiac, orthopedic, and spinal procedures), more comprehensive vaccination strategies are worth exploring. Patients being discharged from the hospital represent an important vaccine target group given their propensity to develop invasive S. aureus infections. Likewise, earlier review of available surveillance data in the U.S. suggest similar epidemiology for C. difficile infections, with the addition of long-term care residence as a susceptible population that should be considered.

Disclaimer
‘The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention/the Agency for Toxic Substances and Disease Registry.’
What are the major issues in pediatric nosocomial infections, and could vaccines be deployed effectively in this population?

**Gregory PRIEBE**
Division of Critical Care Medicine, Children’s Hospital Boston, Channing Laboratory, Brigham and Women’s Hospital - USA

Like adults, pediatric patients with critical illness are susceptible to nosocomial infections, most commonly central line associated bloodstream infection (CLABSI), ventilator-associated pneumonia (VAP), and catheter-associated UTI (CA-UTI). For adults and pediatrics alike, nosocomial infection rates, particularly of CLABSI and CA-UTI, have been linked to pay-for-performance measures as well as nonpayment by both federal and private insurers in the U.S., thereby raising considerable attention of hospital administrators. Data from the CDC’s National Healthcare Safety Network (NHSN) report of 2010 (2009 data) show that CLABSI rates are consistently higher (18-108% higher) in pediatric ICUs compared to adult ICUs having similar patient characteristics (e.g. medical, medical-surgical, or surgical cardiothoracic). This is likely related to several factors, including longer duration of use of central lines in pediatric patients due to limited venous access. Low birthweight (<750 g) premature infants in NICUs have the highest overall CLABSI rates among ICU patients (3.4, compared with the rates of 1.2-2.6 in all other adult and pediatric ICUs). Vaccine approaches in newborns need to focus on passive therapy with antibody due to the low immune response of newborns, particularly premature infants, to typical vaccines (whether polysaccharide or conjugate). Pediatric hematology/oncology patients (non-ICU) have a particularly high rate of CLABSI (3.0 with permanent central lines, 4.8 with temporary lines), although it should be noted that it is often not possible to differentiate a true catheter-related infection from BSI due to gut translocation of bacteria during periods of neutropenia. Regardless of the actual definition, these are significant infections and warrant vaccine approaches although vaccines in these patients are limited by the deficiencies in key immune effectors, which limit responses to active vaccination and interfere with antibodies that rely on opsonophagocytosis by neutrophils.
Suite

Another pediatric population with very high CLABSI rates includes patients with short-bowel syndrome who are dependent on parenteral nutrition. The focus on central line insertion and maintenance “bundles” of evidence-based (or consensus-based) best practices around central line insertion and care have led to reductions in CLABSIs in both pediatric and neonatal ICU populations similar to those initially reported in adult ICU patients. Nevertheless, despite implementation of these bundles, most pediatric ICUs still observe roughly 1 CLABSI every 1-2 months, which for most large PICUs leads to rates of 1-2 CLABSI/1000 patient days. Because the pathogens causing CLABSI are diverse (S. aureus, S. epidermidis, various GNR, and Candida being the most common), multiple vaccines or cocktails of antibodies would need to be used. Vaccine approaches for CA-UTI, for which adults and children have similar rates and causative pathogens, are unlikely to be effective since most of these infections are due to local overgrowth on the catheter in the bladder, where immune effectors are unlikely to have much efficacy.

VAP rates in pediatric ICUs are roughly about half those in adult ICUs (1 vs. 2), with the exception of premature infants (BW <750g), which are closer to 2, although the diagnosis of VAP based on chest x-ray changes is often problematic and equivocal. Vaccine approaches for VAP could focus on the most susceptible populations for active vaccination (those scheduled for major surgery or at risk for trauma such as military, firefighters, police) and the most common pathogens (S. aureus and P. aeruginosa). Passive therapies could be administered on admission to the ICU.

My laboratory has focused on vaccines for VAP, in particular VAP due to the Gram-negative pathogen Pseudomonas aeruginosa, which is the most common Gram-negative cause of VAP in adults and the overall most common cause of VAP in pediatric patients. Although LPS-directed antibody can be protective, it is generally protective only against P. aeruginosa strains having the same LPS O antigen (called serogroup homologous). We have shown using mouse models that the T helper cell derived cytokine IL-17, which recruits neutrophils to the lung, is critical for protection from P. aeruginosa pneumonia by a live-attenuated vaccine when opsonophagocytic antibodies are low or absent. A screen of a P. aeruginosa protein library for proteins that stimulate IL-17-secreting T cells (called Th17 cells) has uncovered several protein antigens that are protective against pneumonia in mice when used as intranasal vaccines.
Session 2

How host systems failure and microbial virulence conspire to perpetuate the problem of nosocomial infections
The Innate Immune System: what it does, how it fails in patients at risk for nosocomial infections

Thierry CALANDRA
Infectious Diseases Service, Department of Medicine
Centre Hospitalier Universitaire Vaudois, University of Lausanne
Switzerland

Microbial sensing and eradication of invasive pathogens are fundamental features of the immune system. Proposed 20 years ago, the concept of pathogen sensing by germ-line encoded pattern recognition receptors (PRRs) has had a major influence on the development of our current understanding of microbial recognition by the innate immune system (1, 2). Microbes are sensed by sentinel cells (primarily macrophages and dendritic cells) that detect microbe/pathogen-associated molecular patterns (MAMPs/PAMPs) (such as endotoxin, peptidoglycan, lipopeptides, flagellin, glucans, mannans, or nucleic acids). Foreign material (noxious compounds or irritants) or endogenous molecules (such as RNA, DNA, ATP, uric acid, HSP) released by damaged tissues also activate innate immune cells (3). The term “danger signals” is now often used to encompass both microbe/pathogen- and damage-associated molecular patterns. Sensing of microbes or activation of cells by danger signals involves the coordinated actions of soluble and cell-associated molecules that are part of the complement system (alternative and mannose-binding lectin pathways), the family of acute phase proteins (such as the LPS binding protein, LBP) and of PRRs including Toll-like receptors (TLRs), nucleotide-binding oligomerization domain-like receptors (NLRs), retinoic acid-inducible gene I (RIG-I) like receptors, C-type lectin receptors (CLRs) and scavenger receptors (4-6). Microbial and endogenous agonists activate various pattern-recognition receptors (PRRs) and signaling pathways which explain why they differ in their capacity to stimulate inflammation, tissue repair or adaptive immunity (7). The mitogen-activated protein kinase (MAPK), nuclear factor (NF)-κB and interferon-related factor (IRF) signal transduction pathways are key components of the intracellular activation machinery leading to the production of effector molecules. Released in the extracellular milieu or expressed as cell-associated co-stimulatory molecules, these mediators are critical for activating innate and adaptive immunity. Cytokines play an essential role in this process acting as orchestrators of the cellular and humoral responses required to eliminate or contain invading pathogens (8).
Suite

Controlling the host inflammatory response is a delicate balancing act. Dysregulated innate immune responses, both by default or by excess, may have dramatic consequences for the host. Nosocomial infections can therefore be seen as a failure to sense and fend off colonizing or invading microorganisms. Tight regulation of innate immunity is thus essential for controlling microbial invasion or cellular responses induced by danger signals and for ensuring a prompt return to homeostasis.

References

Adaptive immunity: what do we know about acquired human immunity to major nosocomial pathogens that can guide vaccine development

Joanna B. GOLDBERG
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University of Virginia, Charlottesville - USA

Gram-negative bacteria remain a continuous threat to the health of hospitalized patients. These individuals are particularly susceptible to infections with bacteria that normal healthy individuals are able to resist. Enterobacteriaceae and *Pseudomonas aeruginosa* are prominent and can cause devastating infections in these individuals. Vaccination would appear an appropriate response to combat this threat, however to date, there are no approved vaccines available that target these bacteria.

Different types of vaccines have been evaluated in mouse models of infection, and the results of these, as well as human trials, will be summarized. Challenges to these efforts include utilizing protocols that accurately mimic the clinical situation of hospitalized patients. Further, the development and validation of assays that represent effective correlates of immunity, including *in vitro* opsonophagocytic and bactericidal killing mediated by antibody and complement, are required. The efficacy of these approaches is a necessary prerequisite prior to testing in humans, including susceptible individuals.
Humoral immunity and carriage of nasopharyngeal pathogens

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The human nasopharynx is an ecological niche hosting a large diversity of bacterial species. Among them there are several that are of clinical importance. These include *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis* and *Staphylococcus aureus*. Microbiological and immunological studies, combining assessment of the presence of (combinations of) these bacterial species in certain human hosts and the immunological response of the host to such colonization is of importance in defining adequate vaccines and vaccination requirements. We performed such studies in adults and children and in addition monitored demographic, clinical and epidemiological features of the populations.

For *S. aureus* it has thus been shown that nasopharyngeal colonization or minor (sub)clinical infections elicit a significant antigen-specific antibody response in persistent carriers of *S. aureus*. However, this antibody response is not sufficient to eliminate *S. aureus* from the nasopharynx. Maternally derived IgG antibodies specifically directed at the same staphylococcal antigens do not protect young infants against *S. aureus* nasal colonization. Despite the significant levels of anti-staphylococcal antibodies in humans, they are still susceptible to *S. aureus* infection. In contrast, antibodies directed against certain *S. aureus* components can protect against nasal colonization or infection in animal models. Apparently, this can not be extrapolated to the situation in humans and hence it will be difficult to treat *S. aureus* colonization or infection with antibody-mediated therapies.

Similar analyses were performed for the other three bacterial colonizers identified above. The presentation will summarize the most salient findings and discuss and integrate these findings from the perspective of infection prevention through natural immunity to these bacteria.
Developing a broadly protective vaccine against *Staphylococcus aureus*

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*Staphylococcus aureus* is one of the most frequent nosocomial infections worldwide and is a leading cause of bloodstream, lower respiratory tract, skin and soft tissue infections. Multidrug resistant strains are emerging and current antibiotics are not efficacious against such strains. Therefore, there is an urgent need to develop vaccines to face this pathogen. However, both active and passive immunization strategies against *S. aureus* have so far failed to show efficacy in humans. Herein, we show a novel approach which targets different toxicity and virulence mechanisms combining three secreted factors and two surface proteins identified by a Reverse Vaccinology approach mainly based on *in silico* analysis as well as proteomics. The selected antigens have different functions, properties, and expression profile. Furthermore, they were shown to be expressed in infected mice. The combination of them was tested in three animal models using a panel of epidemiologically relevant *S. aureus* strains to challenge the mice. The combination gave greater and broader protection than any single antigen tested. Protection appeared associated with functional antibodies which were shown to mediate opsonophagocytosis of the bacterium, protect mice against the infection in passive transfer experiments, and inhibit the function of two components of the vaccine. The diverse functional roles of each of the antigens that we have chosen, and the synergistic and broad protection induced by the antigen combination is expected to address the wide range of diseases associated with *S. aureus*. 
Lines, tubes and protheses: How are they going to affect vaccine development?

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Successful vaccines for prevention of community-acquired infection block local invasion and multiplication of the pathogen, however, most nosocomial infections are associated pathophysiologically with invasive medical devices, such as vascular catheters (CRBSI), endotracheal tubes (VAP), urinary catheters (CAUTI), or tubes (ventriculitis), and the formation of a biofilm on the surface of the device is a fundamental step in the evolution of invasive infection. Biofilms are highly resistant to host defenses and antiinfective therapy, and the question can legitimately be raised, will it be possible to develop vaccines to prevent bacterial and fungal nosocomial infection since the majority are causally associated with implanted catheters, tubes or other implanted devices?

It must first be recognized that nearly all device-associated nosocomial infections are preceded by mucosal or cutaneous colonization by the bacterial or fungal pathogen, which may be present at admission or occurs during hospitalization, and the colonizing microorganism adheres to the surface and forms a biofilm on the device following implantation. Thus, in theory, it should be possible to develop vaccines for prevention of nosocomial infection to prevent mucocutaneous colonization, similar to the vaccines for prevention of community-acquired infection unassociated with invasive devices.

However, it is not implausible that it will not be possible to develop vaccines that can block mucocutaneous colonization by the pathogens encountered in device-associated infection, staphylococci, enterococci, gram-negative bacilli or Candida spp, since these organisms are normal flora and may not be eradicable by host defense mechanisms. The question then becomes, might it be possible to develop vaccines that can block invasion of surface-colonizing microorganisms or that can block biofilm formation?
Experimental data from human trials of novel vaccines for prevention of UTI have shown promising efficacy in the setting of established periurethral colonization by bacterial uropathogens. Moreover, the high-level protection of a novel *Staphylococcus aureus* vaccine targeting a novel planktonic surface antigen seen in an animal model of CRBSI and the modest but significant efficacy of a human capsular polysaccharide *S. aureus* vaccine in a comparative trial in dialysis patients, who are often heavily colonized by *S. aureus*, further suggest that it should be possible to develop vaccines to provide protection against biofilm-associated nosocomial infections of medical devices, even in the setting of heavy preexistent mucocutaneous colonization.

As regards vaccines for inhibition of biofilm formation, we have experimental data from an animal model showing that a novel vaccine targeting a coagulase-negative staphylococcal adhesin can prevent CRBSI, suggesting that efforts to target critical biofilm-rather than planktonic-phase antigens should be feasible.

In sum, I believe that it should be possible to develop effective vaccines that can prevent nosocomial infections, including the many which derive from catheters, tubes and other implanted invasive medical devices. The greatest challenge may prove to be achieving protective levels of vaccine immunogenicity in patients immunosuppressed by their diseases, their treatments or malnutrition.
Active and passive immunization strategies

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Active and passive immunization strategies are two approaches to confer immunity and each has advantages and disadvantages. Active immunization can elicit a long lasting immune response that is protective but takes time, is ultimately reliant on the status of the immune system and hosts with impaired immunity may not produce the optimal antibody responses. Furthermore, the immune response that results from active immunization has emergent properties and may not be protective or even deleterious. Passive immunization has the advantage of delivering only the desired antibody to the host and thus is the only option available for giving a host immediate immunity but it is expensive, difficult to administer, and transient. Both active and passive immunization strategies rely on antibodies as effector molecules. Although the function of antibody has been thought to be well understood there is now increasing evidence for action beyond the classical mechanisms such as opsonization, complement activation, viral and toxin neutralization and antibody-dependent cellular cytotoxicity. The talk will present a new synthesis for antibody mediated immunity that integrates the older functions with newly described functions such as immunomodulation, activation of pathogen gene expression, inhibition of biofilm formation, and direct pathogen cytotoxicity.
Session 3

Gram negative bacterial pathogens: the more untreatable they become the more we need immunotherapeutic options
Innate immune surveillance; examples from infection and cancer

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We have identified beneficial and destructive forces of innate immunity, which influence the severity of Urinary tract infection (UTI). Genetic variation either exaggerates the severity of acute pyelonephritis to include urosepsis and renal scarring or protects against symptomatic disease by suppressing innate immune signaling, as in asymptomatic bacteriuria (for review see Ragnarsdottir, Nature Reviews Urology, 2011).

I. Dysregulated innate immunity, severe acute disease and chronic tissue damage. In acute pyelonephritis strains, P fimbriae are direct, molecular activators of TLR4 signaling. Downstream signaling involves the phosphorylation of mitogen-activated protein kinases, phospholipase Cγ, p38, JNK, CREB and FOS–JUN, leading to IRF3- and AP-1 dependent transcription of innate immune response genes. A single Irf3 deletion causes urosepsis with high mortality and renal pathology in Irf3-/- mice. IRF3 promoter polymorphisms differ between children with severe, symptomatic UTI or ABU and IRF3 promoter activity is reduced by the pyelonephritis-associated genotype, consistent with the pathology in Irf3-/- mice (Fischer, PLoS Pathogens, 2010).

II. Low TLR4, innate immune unresponsiveness and protection from severe disease. Mice lacking functional Tlr4, develop an ABU like state and the early innate immune response to UTI is low or absent. Children with ABU express less TLR4 than APN prone children or controls but do not carry structural gene mutations explaining this phenotype. We have identified eight TLR4 promoter sequence variants, forming 19 haplotypes and 29 genotype patterns. The ABU-associated genotypes reduced TLR4 expression and the response to infection (Ragnarsdottir, J Infect Dis, 2007, PLoS One, 2010). Host susceptibility to common infections like UTI may thus be strongly influenced by single gene modifications affecting the innate immune response.
Suite

III. Host imprinting on bacterial genomes – rapid, divergent evolution in individual hosts. Bacteria lose or gain genetic material and through selection, new variants become fixed in the population. We have studied for the first time the genome-wide evolution of a single bacterial strain in different human hosts, using the therapeutic human inoculation model. The complete genome sequence of the prototype asymptomatic bacteriuria strain *E. coli* 83972 has been obtained and compared to the genomes of re-isolates from several patients after therapeutic bladder colonization. Genetic alterations included metabolic and virulence related genes and often affected pleiotropic regulators of bacterial gene expression. The results suggest that evolution in this case favors “commensalism” rather than virulence, through the loss of genetic material (Zdziarski, PLoS Pathogens, 2010).

UTIs are so common and costly that UTI-prone patients and their quality of care should be of major concern. Why UTI patients rarely receive the diagnostic and therapeutic attention given to other severe infectious diseases with considerably lower frequencies is not clear. Molecular data on host and pathogen is now available to aid in the diagnostic and therapeutic decisions taken in this patient group.
The issue of anti-endotoxin vaccines

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Gram-negative bacterial (GNB) sepsis remains a lethal condition with mortality rates often in excess of 30%. With the increasing antimicrobial resistance among these pathogens, there have been ongoing efforts to develop immunomodulatory adjunctive therapies. Early successes reported with vaccines designed to induce antibodies against highly conserved regions of the GNB endotoxin core glycolipid were difficult to reproduce and led to interest in other modalities. Given the lack of success of cytokine modulators and LPS receptor antagonists, it may be time to reconsider anti-endotoxin antibodies. Originally, polyvalent, O-directed vaccines were considered not to be feasible because of the large number of O-serogroups among major GNB pathogens: however, since only a few O-serogroups are capable of causing invasive infection, this assumption must be re-assessed. Passive therapy with core glycolipid antisera was successful in both pre-clinical and clinical studies, but later studies were unable to confirm this efficacy. Review of those studies, however, suggest that insufficient amounts of anti-core endotoxin antibody were administered, thereby leaving this hypothesis still untested. We developed an anti-core endotoxin subunit vaccine comprised of detoxified LPS from the \textit{E. coli} J5 LPS complexed with group B meningococcal OMP (J5dLPS/OMP). The vaccine was efficacious in multiple animal models of sepsis when antibodies were elicited actively or administered passively. It was safe and well-tolerated in phase 1 clinical studies and will soon undergo additional phase 1 testing in combination with an adjuvant. Given the emerging data that patients who survive an episode of sepsis do poorly over the long term, it is critical that prevention of sepsis in target populations with active immunization be considered. In this regard, novel strategies for immunization of at risk populations must be developed for not only this vaccine but for similar vaccines directed towards nosocomial infections, such as MRSA.
Acinetobacter: What we know and what might be done

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Acinetobacter baumannii has emerged globally in the last decade as a highly troublesome nosocomial pathogen especially in intensive care units (ICUs) and among immunocompromised patients. Treatment is complicated by high rates of resistance to multiple antibiotics which translates into extended lengths of stays in ICUs and mortality. With few effective antibiotics for the treatment of infections caused by multidrug resistant A. baumannii on the horizon the need for immunotherapeutic alternatives to combat this pathogen in more urgent than ever. We have identified a novel surface adhesin of A. baumannii designated as the Acinetobacter trimeric autotransporter (Ata) protein that is highly distributed and conserved among clinical isolates. Ata binds to various extracellular matrix components including collagens type I, III, IV, V and laminin and is an important factor for complement resistance, biofilm formation and promotes the survival of A. baumannii in lung, bloodstream and wound infections in mice. Ata also contributes to extrapulmonary dissemination of A. baumannii into the bloodstream and mediates the binding of A. baumannii to collagen type IV. This latter binding can be specifically inhibited with antibodies to Ata. Additionally, we demonstrate that in the presence of human complement and polymorphonuclear cells (PMNs), antibodies to Ata are highly opsonic against A. baumannii 17978. Moreover, in the absence of PMNs, antisera to Ata promotes complement-mediated bactericidal killing of A. baumannii 17978 and another eight additional heterologous isolates expressing various levels of surface Ata. Finally, antisera to Ata is protective in a mouse model of pneumonia using immunocompetent and neutropenic mice challenged with three strains of A. baumannii, wild type 17978 and two multi drug resistant (MDR) isolates. The ability of Ata to engender anti-adhesive, bactericidal, opsonophagocytic and protective antibodies validates its use as an immunotherapeutic target against MDR A. baumannii infections.
Session 4

Gram positive bacterial pathogens: they just won’t go away
**Staphylococcus aureus: where do we stand in our understanding of virulence and immunity?**

Bachra ROKBI  
Sanofi Pasteur - FRANCE

*Staphylococcus aureus* is one of the leading causes of both community-associated and nosocomial infections worldwide. As a commensal organism, *S. aureus* resides in the human skin and nares. Despite constant exposure through colonization, the majority of the human population does not succumb to severe invasive infections with *S. aureus*. As is the case for other Gram-positive bacteria, immune clearance of *S. aureus* is thought to be mediated by complement fixation and opsonophagocytosis via antibodies that recognize the bacterial cell surface components. In addition to antibody responses, phagocytes such as polymorphonuclear neutrophils (PMNs) are critical for opsonophagocytic clearance of *S. aureus* and a key determinant in the course of disease. Additional studies suggest that *S. aureus*-specific T cells play a key role in the outcome of infection by regulating CXC chemokine production and associated PMN recruitment. However, under certain circumstances *S. aureus* continues to progress inside the host despite the host immune defenses resulting in a persistent infection. *S. aureus* is a complex organism with numerous components that can either act together or on their own to contribute to the pathogenesis of infection. The many virulence factors that the organism can produce also have a role in enabling the organism to evade immune responses and subsequent clearance. The interplay between *S. aureus* virulence factors and host innate and adaptive immune responses will be discussed during the presentation.
S. aureus vaccines: vaccines everywhere: yet not one works yet. Why?

Jean C. LEE
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Numerous single-component S. aureus vaccines or immunotherapies have failed to meet their clinical endpoints in human phase III clinical trials: a capsular polysaccharide-based vaccine (StaphVAX), a human IgG preparation (Veronate) with elevated levels of antibodies to clumping factor A, a S. aureus protein (IsdB) vaccine, and a humanized monoclonal antibody to lipoteichoic acid. There is no evidence that natural infection by S. aureus leads to an adaptive immune response that protects against re-infection. Thus, inducing immunity to S. aureus by a vaccine approach presents a unique challenge. Given the multiple and often redundant nature of staphylococcal virulence factors that promote pathogenesis, if a vaccine is to prove effective, it will most likely be comprised of multiple components. Likely candidates include cell wall-associated proteins, secreted toxoids, and surface polysaccharides. A thorough understanding of the immune correlates of protection against S. aureus infection is sought, but this is accomplished in large part by preclinical vaccination studies in imperfect rodent models of staphylococcal disease. Whether the data obtained in these preclinical studies will predict protection against infection in humans is uncertain. Phase I and II clinical trials in progress test multicomponent vaccines designed to elicit opsonic and toxin-neutralizing antibodies, as well as memory T cells capable of enhancing phagocyte recruitment to sites of infection, thereby facilitating clearance of the organism from tissues. Only by testing this second-generation vaccine approach against S. aureus in phase III clinical trials will its merit be demonstrated.
Coagulase-Negative Staphylococci: can we do it and would we use it?

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Coagulase-negative staphylococci with the most important species Staphylococcus epidermidis are omnipresent colonizers of the human skin and mucous surfaces, but may cause moderately severe to severe, commonly chronic infections after penetration of the epithelial barrier. Frequently they are introduced into the human body as contaminants on indwelling medical devices during surgical intervention in hospitals. Antibiotic resistance, especially to methicillin, is frequent in S. epidermidis; therefore, novel methods of therapeutic intervention are being explored. These include target-oriented drug development and vaccines against components of the S. epidermidis surface, such as exopolysaccharide, surface proteins, and other surface polymers. However, several findings from basic research call for caution when exploring such approaches. First, recent studies suggest that there are no S. epidermidis components exclusively linked to invasiveness. Furthermore, S. epidermidis and other CNS may have an important function in balancing the human microflora and minimizing colonization with aggressive strains such as S. aureus.
Possible vaccine targets in for enterococcal infections: The enterococcal cell wall revisited

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Germany

Enterococci are among the most prevalent pathogens causing nosocomial infections. Especially E. faecium is a rising threat, and strains with resistances to all clinically available antibiotics are not uncommon. We have previously shown that lipoteichoic acid (LTA) is a target of opsonic antibodies in E. faecalis and E. faecium. Recent data from our group indicate that antibodies against enterococcal LTA are cross-reactive and cross-protective against several other gram-positive pathogens. We have identified the poly-glycerol backbone of the LTA molecule as the target of opsonic antibodies and have proposed a simplified procedure to synthetically produce LTA mimetics. Additional work from our group has identified several protein antigens that may be used as vaccine targets, either alone, or conjugated to a suitable polysaccharide surface antigen. Our results suggest that several possible vaccine targets against enterococci exist. Additional studies are under way to better understand the distribution of these antigens in clinical isolates, and to define an optimal combination of antigens to successfully combat these infections.
Clostridium difficile: are we making progress?

Ginamarie FOGLIA
Sanofi Pasteur - USA

_Clostridium difficile_ infection (CDI) is the most common nosocomial infection in Europe and North America, and has also now spread to communities outside the hospital environment. In response to the increasing disease burden of _C. difficile_-associated diarrhoea, Sanofi Pasteur is currently undertaking the clinical development of a vaccine for primary disease prevention. The candidate is a toxoid vaccine, designed to stimulate immunity against exotoxins A and B, which are secreted by the _C. difficile_ bacterium. These toxins are highly injurious to the human colon, causing enterocyte cell death, a marked acute inflammatory response and severe mucosal injury. Results from Phase I studies in healthy adult (18-55 years) and elderly (≥65 years) volunteers have been encouraging. The candidate vaccine has been well tolerated and highly immunogenic against exotoxins A and B. A subsequent dose-ranging, Phase II study, with primary objectives to further describe the safety and immunogenicity of the candidate vaccine and also to record the occurrence of first-time CDI episodes, is now actively enrolling 650 participants. Data from this study - the first of which will be available later in 2011 – will assist in Phase III development. Development of this vaccine is a priority at Sanofi Pasteur. Although still at an early stage, results with this vaccine are encouraging and support continued clinical development for the primary prevention of _C. difficile_-associated diarrhoea.
Session 5

Targeting viral and fungal nosocomial pathogens for vaccination
Possibilities for vaccination against viral causes of nosocomial respiratory infections

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Abstract not provided
Possibilities for vaccination against the viral causes of nosocomial gastrointestinal infections

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Rotavirus, the major cause of severe acute dehydrating gastroenteritis in children less than 5 years of age, is responsible for an estimated 20-50% of all hospitalizations for diarrhea and approximately 440,000 deaths annually, primarily in the developing world. Rotavirus vaccines are considered the most promising means for disease prevention. While the prime rationale for developing rotavirus vaccines has been the enormous burden of rotavirus infection leading to severe and fatal disease, a secondary benefit may be the prevention of nosocomial rotavirus diarrhea.
Opportunistic and endemic mycoses: The likelihood of vaccinating against these complex fungal pathogens

David STEVENS
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Although there is considerable experimental data to support the idea, bringing a fungal vaccine to fruition has been elusive. Moreover, vaccinating the immunocompromised, susceptible to an opportunistic disease such as invasive aspergillosis, seems formidable. However, pioneering studies using *Aspergillus* particulate forms or homogenates, and recently, recombinant proteins, have demonstrated feasibility. Moreover, T cell receptors also recognize glycotopes if presented in the appropriate MHC-binding context. The potential role of induced antibody has been appreciated only recently.

Recent studies in our laboratory with heat-killed Saccharomyces (HKY) have raised the possibility of development of a panfungal vaccine. This yeast may be nature’s experimental reagent, to show the way to a protective protein-carbohydrate conjugate vaccine. Subcutaneous HKY is an effective vaccine against *Aspergillus, Coccidioides* or *Candida* challenge.

We have learned the protective moiety is in the cell wall, and proteins, glucan and lipid all seem important. We have also found the cell wall glycans alone, mannan or glucan, as a vaccine each provide significant protection. This leads to consideration of the importance of glycosylated proteins and glycan polymer-protein conjugates in vaccine development. We think the most productive route to a fungal-specific vaccine may be a conjugate vaccine that combines the optimally configured glycan with a specific immunogenic protein. Our work so far suggests that some proteins may be sufficiently cross-immunogenic, such that combined with the appropriate glycan, it may be possible to develop a pan-fungal vaccine.
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This meeting was made possible through unrestricted educational grants from Sanofi Pasteur.