8 April 2010

This supplement has been prepared to present scientific and technical news items that may be of more interest to technical personnel at RDT&E activities and the labs, or the medics rather than the broader readership of the basic CB Daily. Due to the nature of the material, the articles, if available online, are usually only available through subscription services thus making specific links generally unavailable. Thus, usually only the bibliographic citation is available for use by an activity's technical library.

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Chem-Bio News – S&T Edition

1. METALLOPORPHYRINS-MODIFIED CARBON NANOTUBES NETWORKED FILMS-BASED CHEMICAL SENSORS FOR ENHANCED GAS SENSITIVITY: *"These findings are then promising for the development of arrays of CNT-based gas nanosensors with broad selectivities for fingerprinting analysis of complex samples."*

2. A GENOMIC SURVEY OF POSITIVE SELECTION IN BURKHOLDERIA PSEUDOMALLEI PROVIDES INSIGHTS INTO THE EVOLUTION OF ACCIDENTAL VIRULENCE: *"We found evidence for the existence of several new genes in the Bp reference genome, identifying 282 novel genes supported by at least two independent lines of supporting evidence (mRNA transcripts, database homologs, and presence of ribosomal binding sites) and 81 novel genes supported by all three lines."*

3. BIO-ASSEMBLER USES MAGNETIC LEVITATION TO ASSEMBLE 3-D CELL CULTURES: *"Most conventional petri dish based cell culture techniques produce monolayers cell growth that is missing essential cellular functions that are present in living organisms; gene expression, signaling and morphology can be different and this compromises its clinical relevance. It limits their potential to predict the cellular responses of real organisms. One major impact of cell cultures that more closely resemble native tissue will be better results for preclinical drug tests."*

4. USE OF NOROVIRUS GENOTYPE PROFILES TO DIFFERENTIATE ORIGINS OF FOODBORNE OUTBREAKS: *"On the basis of the 5-year strain collections, some genotypes (I.2 and I.4) suggest FB [foodborne] instead of PB[peopleborne] preference, and others (II.2 and II.6/II.7) are commonly seen in outbreaks but not detected in bivalve mollusks (and FB-food). Strains detected in food that caused outbreaks (FB-food) showed a genotype profile similar to those in bivalve mollusk monitoring and dissimilar to the profile detected in human feces (i.e., FB-feces, FHB, PB, UN) with respect to the frequently seen genotypes."*

5. IMMUNE CELLS FIGHT OFF NANOTUBES: *"Carbon nanotubes can be degraded by an enzyme found in human immune cells, report US researchers. The results suggest that nanotubes - which may find use in a range of applications spanning medicine and materials - may not be as harmful to human health as previously feared."*

6. AN ATTRACTIVE METHOD FOR BACTERIA DETECTION: *"Pieters' team attached commercially available magnetic beads containing the protein streptavidin to a series of carbohydrates that were specially designed to bind to the bacterium's proteins. After mixing with the bacterium, the bacteria-bead conjugates could simply be removed using a magnet and the amount determined using a luminescence assay."*

7. IN SILICO PHARMACOPHORE MODEL FOR TABUN-INHIBITED ACETYLCHOLINESTERASE REACTIVATORS: A STUDY OF THEIR STEREOELECTRONIC PROPERTIES: *"These results provided the first predictive pharmacophore model of oxime affinity for binding toward GA-inhibited AChE."*

8. DEVELOPMENT OF A HIGH-THROUGHPUT SCREENING FOR NERVE AGENT DETOXIFYING MATERIALS USING A FULLY-AUTOMATED ROBOT-ASSISTED BIOLOGICAL ASSAY: *"Here we introduce a robot-assisted liquid handling system with warming, cooling and incubating facilities to screen the detoxifying properties of biological and chemical materials against nerve agents."*

9. A LYOPHILIZED FORMULATION OF RIVAX, A RECOMBINANT RICIN SUBUNIT VACCINE, RETAINS IMMUNOGENICITY: *"We have now developed a lyophilized formulation and demonstrated stability and efficacy for at least 1 year stored refrigerated or at room temperature administered with or without alum."*

CB Daily Report

Chem-Bio News

METALLOPORPHYRINS-MODIFIED CARBON NANOTUBES NETWORKED FILMS-BASED CHEMICAL SENSORS FOR ENHANCED GAS SENSITIVITY
Journal of Technology & Science
April 11, 2010

"Modified film exhibits an increased sensitivity of the electrical resistance towards the concentrations of common volatile Compounds (alcohols, amines, aromatic and ketones), at room temperature."

"Furthermore, a part of the adsorption properties of the functional units is transferred to the sensor signal and, as a consequence, the selectivity of the sensor is also modified. Principal Component Analysis (PCA) demonstrates that the functionalization provides enough selectivity change to turn a triplicate of the same CNT film into an effective sensor array capable of the compounds recognition."

"These findings are then promising for the development of arrays of CNT-based gas nanosensors with broad selectivities for fingerprinting analysis of complex samples."

The full article can be found at: (M. Penza, et. al., "Metalloporphyrins-modified carbon nanotubes networked films-based chemical sensors for enhanced gas sensitivity". Sensors and Actuators B - Chemical, 2010;144(2 Sp. Iss.):387-394). Link not available.

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A GENOMIC SURVEY OF POSITIVE SELECTION IN BURKHOLDERIA PSEUDOMALLEI PROVIDES INSIGHTS INTO THE EVOLUTION OF ACCIDENTAL VIRULENCE

By Tannistha Nandi, Catherine Ong, Arvind Pratap Singh, Justin Boddey, Timothy Atkins, Mitali Sarkar-Tyson, Angela E. Essex-Lopresti, Hui Hoon Chua, Talima Pearson, Jason F. Kreisberg, Christina Nilsson, Pramila Ariyaratne, Catherine Ronning, Liliana Losada, Yijun Ruan, Wing-Kin Sung, Donald Woods, Richard W. Titball, Ifor Beacham, Ian Peak, Paul Keim, William C. Nierman, Patrick Tan

PLoS Pathogens
April 01, 2010

“Abstract

Certain environmental microorganisms can cause severe human infections, even in the absence of an obvious requirement for transition through an animal host for replication (“accidental virulence”). To understand this process, we compared eleven isolate genomes of Burkholderia pseudomallei (Bp), a tropical soil microbe and causative agent of the human and animal disease melioidosis. We found evidence for the existence of several new genes in the Bp reference genome, identifying 282 novel genes supported by at least two independent lines of supporting evidence (mRNA transcripts, database homologs, and presence of ribosomal binding sites) and 81 novel genes supported by all three lines. Within the Bp core genome, 211 genes exhibited significant levels of positive selection (4.5%), distributed across many cellular pathways including carbohydrate and secondary metabolism. Functional experiments revealed that certain positively selected genes might enhance mammalian virulence by interacting with host cellular pathways or utilizing host nutrients. Evolutionary modifications improving Bp environmental fitness may thus have indirectly facilitated the ability of Bp to colonize and survive in mammalian hosts. These findings improve our understanding of the pathogenesis of melioidosis, and establish Bp as a model system for studying the genetics of accidental virulence.”

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“Author Summary

With recent advances in genomics now permitting the systematic comparison of dozens, if not hundreds, of closely related bacterial strains, the opportunity arises for developing novel approaches to identify the complete repertoire of molecular factors governing interactions between hosts and pathogens. We explored these approaches using the model system Burkholderia pseudomallei (Bp), a Gram-negative bacterium that causes the tropical disease melioidosis. At 7.2 Mb, the Bp genome represents one of the most complex bacterial genomes sequenced to date. In this study, we present the first nucleotide-resolution comparative analysis of a panel of sequenced Bp strains. We identified a novel panel of genes demonstrating “positive selection”, referring to functional adaptations related to survival in soil, the natural reservoir of Bp. We propose a model and provide functional evidence that some of these genes may also have indirectly facilitated the ability of Bp to

colonize and infect a mammalian host."

…..

"In our analysis, we have proposed that many of the genetic alterations observed in the positively selected genes were primarily driven by environmental pressures outside the human or mammalian host. Nevertheless, if Bp undergoes cryptic cycling through normal humans or other potential mammalian hosts, such as livestock or wild cattle [59], it remains possible that certain survival and virulence traits were directly selected for in mammals. In melioidosis-endemic NE Thailand, the majority of healthy individuals have antibodies to Bp by the age of 4 years, indicating constant exposure to the bacterium that may occur by inoculation, inhalation or ingestion [4]. Within such hosts, Bp might spend periods of time being exposed to the mammalian immune response and various physiologic traits. Subsequent return to the environment in a viable state, through skin desquamation or in urine and stool, could also lead to the selection of factors that promote survival in vivo. However, because we a) consider the mammalian host to be a relatively minor component of Bp ecology, b) such cryptic cycling through mammalian hosts has yet to be documented, and c) the lack of genetic variation between the primary and relapsed strains suggests that the Bp genome is likely to exhibit a high degree of stability during mammalian infection, we argue that this scenario is, on balance, possible but less likely."

The full article can be found at: http://www.plospathogens.org/article/info%3Adoi%2F10.1371%2Fjournal.ppat.1000845;jsessionid=86512079D7627B232A5611BC6AE69142

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BIO-ASSEMBLER USES MAGNETIC LEVITATION TO ASSEMBLE 3-D CELL CULTURES
By Michael Berger
Nanowerk.com
March 31, 2010

"Most conventional petri dish based cell culture techniques produce monolayers cell growth that is missing essential cellular functions that are present in living organisms; gene expression, signaling and morphology can be different and this compromises its clinical relevance. It limits their potential to predict the cellular responses of real organisms. One major impact of cell cultures that more closely resemble native tissue will be better results for preclinical drug tests.

In order to develop cellular models that mimic the functions of living tissues, researchers have therefore been trying to move from two-dimensional to three-dimensional (3D) cultures. A recent example is a technique that uses magnetic levitation of cells in the presence of a hydrogel consisting of gold, magnetic iron oxide nanoparticles and filamentous bacteriophage. By spatially controlling the magnetic field while cells divide and grow, the geometry of the cell mass can be manipulated, and multicellular clustering of different cell types in co-culture can be achieved.

This 3-D technique is easy enough for most labs to set up immediately. Compared with cell

cultures grown on flat surfaces, the 3-D cell cultures tend to form tissues that more closely resemble those inside the body.

The magnetic levitation technology provides an alternative to biodegradable porous scaffolds and protein matrices. The researchers, led by Wadih Arap and Renata Pasqualini at The University of Texas M. D. Anderson Cancer Center and Tom Killian at Rice University, explain that biodegradable scaffolds usually may suffer from slow or delayed propagation of cells and establishment of cell–cell interactions. "Existing commercial products are useful and not particularly expensive, but their chemical composition is fixed (that is, unchangeable). In contrast, our bio-assembler allows adaptable magnetic-based cell levitation and may provide for improved three-dimensional cell-growth conditions in certain settings. The methodology is cost-effective, because it does not require a specific medium, and it is compatible with standard two-dimensional cell culture techniques."

To make cells levitate, the research team added magnetic nanoparticles to a gel that contains phage. When cells are added to the gel, the phage causes the particles to be absorbed into cells over a few hours. The gel is then washed away, and the nanoparticle-loaded cells are placed in a petri dish filled with a liquid that promotes cell growth and division. By placing a coin-sized magnet atop the dish's lid, cells could be lifted off the bottom of the dish – now the researchers could concentrate them and allow them to grow and divide while they were suspended in the liquid."

The full article can be found at: http://www.nanowerk.com/spotlight/spotid=15587.php

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USE OF NOROVIRUS GENOTYPE PROFILES TO DIFFERENTIATE ORIGINS OF FOODBORNE OUTBREAKS

By Linda Verhoef, Comments to Author Harry Vennema, Wilfrid van Pelt, David Lees, Hendriek Boshuizen, Kathleen Henshilwood, and Marion Koopmans
Emerging Infectious Diseases
April 2010

"Abstract
Because secondary transmission masks the connection between sources and outbreaks, estimating the proportion of foodborne norovirus infections is difficult. We studied whether norovirus genotype frequency distributions (genotype profiles) can enhance detection of the sources of foodborne outbreaks. Control measures differ substantially; therefore, differentiating this transmission mode from person-borne or food handler–borne outbreaks is of public health interest. Comparison of bivalve mollusks collected during monitoring (n = 295) and outbreak surveillance strains (n = 2,858) showed 2 distinguishable genotype profiles in 1) human feces and 2) source-contaminated food and bivalve mollusks; genotypes I.2 and I.4 were more frequently detected in foodborne outbreaks. Overall, ≈21% of all outbreaks were foodborne; further analysis showed that 25% of the outbreaks reported as food handler–associated were probably caused by source contamination of the food."

…..

“We studied whether the genotype frequency distributions (genotype profiles) of strains can be used to differentiate foodborne outbreaks related to contamination early in the food chain (i.e., during primary production) from those related to contamination later in the food chain (i.e., during preparation or serving). If so, detection of food origins likely to cause geographically disseminated outbreaks will be enhanced. We considered methods for attribution to multiple sources commonly applied to Salmonella infections (13) because different transmission routes involved in norovirus infections can disguise the foodborne origin. However, such methods require strain collections representative of noroviruses in the potential sources that are as yet unavailable because of difficulties in the direct detection of viruses in food (14–16). Therefore, we compared 2 strain collections: noroviruses identified through filter-feeding bivalve mollusk monitoring representing source contamination of food and noroviruses collected through systematic surveillance of illness in the population. The first was collected by the European Community Reference Laboratory for Monitoring Bacteriological and Viral Contamination of Bivalve Mollusks during 1995–2004 (17) and the second by the Food-Borne Viruses in Europe (FBVE) network, which has conducted surveillance for norovirus outbreaks in Europe since 1999. Prior investigation of the FBVE database of systematically collected epidemiologic and microbiological norovirus surveillance data (6) showed that the epidemiology of norovirus outbreaks in Europe varies between genogroups. An analysis of the properties of reported outbreaks indicated a clear difference between GII.4 strains and other noroviruses; non-GII.4 strains were found more frequently in outbreaks with a foodborne mode of transmission, and GII.4 strains were found more frequently in healthcare settings with person-to-person transmission (18,19). Here we demonstrate that further specification into genotypes shows additional differences in the epidemiology of norovirus outbreaks.”

…..

“…..We confirmed a significant difference in the GI:GII ratio; GI strains were more prevalent in bivalve mollusks. On the basis of the 5-year strain collections, some genotypes (I.2 and I.4) suggest FB instead of PB preference, and others (II.2 and II.6/II.7) are commonly seen in outbreaks but not detected in bivalve mollusks (and FB-food). Strains detected in food that caused outbreaks (FB-food) showed a genotype profile similar to those in bivalve mollusk monitoring and dissimilar to the profile detected in human feces (i.e., FB-feces, FHB, PB, UN) with respect to the frequently seen genotypes. This finding may reflect the ability of these genotypes to survive outside humans or their diminished ability to spread or replicate within the human population. Genotype profiles of FHB and UN resulted in diverging association outcomes, which may reflect their potential dual origin.”

The full article can be found at: http://www.cdc.gov/eid/content/16/4/617.htm

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IMMUNE CELLS FIGHT OFF NANOTUBES
By Lewis Brindley
Chemistry World
April 06, 2010

“Carbon nanotubes can be degraded by an enzyme found in human immune cells, report US researchers. The results suggest that nanotubes - which may find use in a range of applications spanning medicine and materials - may not be as harmful to human health as previously feared.

Determining just how toxic carbon nanotubes are has become one of the most pressing questions in nanotechnology, due to the myriad of applications they could be used in. Previous studies have compared nanotubes to asbestos, and just like asbestos fibres, nanotubes are too long to be enveloped by macrophages - the immune cells that usually swallow up invading pathogens. Exposure usually triggers a strong inflammatory response and can eventually lead to lung disease or tumours.

Now, researchers have found that an enzyme called myeloperoxidase, which is present in human immune cells called neutrophils, can break down nanotubes and stop the immune response. The myeloperoxidase enzyme uses hydrogen peroxide to produce hypochlorite and reactive radicals; a potent mixture that usually targets invading bacteria, but has now been found to degrade nanotubes and in the process release CO2 gas.”

The full article can be found at: http://www.rsc.org/chemistryworld/News/2010/April/06041002.asp

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AN ATTRACTIVE METHOD FOR BACTERIA DETECTION
By David Barden
Highlights in Chemical Biology
March 30, 2010

“Rapid identification and characterization of bacterial pathogens for medical diagnosis is important to serve as an alternative to time-consuming culturing. Bacteria carry adhesion proteins on their surface, which bind to cells in the body during the infection process. These adhesion proteins are different between species and so can be used to detect bacteria. Methods to detect E. coli by identifying its adhesion proteins have been successful but until now it has not been extended to other species.

Roland Pieters and colleagues at Utrecht University, The Netherlands, have devised a method to specifically detect the adhesion proteins on Streptococcus suis, which causes meningitis, septicemia, and pneumonia in pigs, and 'has also been identified as an emerging human threat' says Pieters.

Pieters' team attached commercially available magnetic beads containing the protein streptavidin to a series of carbohydrates that were specially designed to bind to the bacterium's proteins. After mixing with the bacterium, the bacteria-bead conjugates could simply be removed using a magnet and the amount determined using a luminescence assay.”

The full article can be found at: http://www.rsc.org/Publishing/Journals/cb/

Volume/2010/05/an_attractive_method.asp

The original article can be found at: http://www.rsc.org/Publishing/Journals/OB/article.asp?doi=c000819b

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IN SILICO PHARMACOPHORE MODEL FOR TABUN-INHIBITED ACETYLCHOLINESTERASE REACTIVATORS: A STUDY OF THEIR STEREOELECTRONIC PROPERTIES

Proteomics Weekly
April 12, 2010

“Inhibited AChE call be reactivated by oximes, antidotes for OP exposure. However, OP intoxication caused by the nerve agent tabun (GA) is particularly resistant to oximes, which poorly reactivate GA-inhibited AChE. In an attempt to develop a rational strategy for the discovery and design of novel reactivators with lower toxicity and increased efficacy in reactivating GA-inhibited ACME, we developed the first in silico pharmacophore model for binding affinity of GA-inhibited AChE from a set of 11 oximes. Oximes were analyzed for stereoelectronic profiles and three-dimensional quantitative structure-activity relationship pharmacophores using ab initio quantum chemical and pharmacophore generation methods. Quantum chemical methods were sequentially used from semiempirical AM1 to hierarchical ab initio Calculations to determine the stereoelectronic properties of nine oximes exhibiting affinity for binding to GA-inhibited AChE in vivo. The Calculated stereoelectronic properties led US to develop the in silico pharmacophore model using CATALYST methodology. Specific stereoelectronic profiles including the distance between bisquarternary nitrogen atoms of the pyridinium ring in the oximes, hydrophilicity, surface area, nucleophilicity of the oxime oxygen, and location of the molecular orbitals on the isosurfaces have important roles for potencies for reactivating GA-inhibited AChE. The in silico pharmacophore model of oxime affinity for binding to GA-inhibited AChE was found to require a hydrogen bond acceptor, a hydrogen bond donor at the two terminal regions, and in aromatic ring in the central region of the oximes. The model was found to be well-correlated (R = 0.9) With experimental oxime affinity for binding to GA-inhibited AChE. Additional sterectelectronic features relating activity with the location of molecular orbitals and weak electrostatic potential field over the aromatic rings were, found to be consistent with the pharmacophore model. These results provided the first predictive pharmacophore model of oxime affinity for binding toward GA-inhibited AChE.”

"The model may be Useful for virtual screening of compound libraries to discover and/or custom synthesize more efficacious and less toxic reactivators that may be useful for GA intoxication."

The full article can be found at: (A.K. Bhattacharjee, et. al., “In Silico Pharmacophore Model for Tabun-Inhibited Acetylcholinesterase Reactivators: A Study of Their Stereoelectronic Properties”. Chemical Research in Toxicology, 2010;23(1):26-36). Link not available.

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DEVELOPMENT OF A HIGH-THROUGHPUT SCREENING FOR NERVE AGENT DETOXIFYING MATERIALS USING A FULLY-AUTOMATED ROBOT-ASSISTED BIOLOGICAL ASSAY
Medical Letter on the CDC & FDA
April 11, 2010

“Here we introduce a robot-assisted liquid handling system with warming, cooling and incubating facilities to screen the detoxifying properties of biological and chemical materials against nerve agents."

"Two biological tests were established and plasma from various species, DFPase and three cyclodextrins were used as test materials. In test 1, plasma was mixed with sarin or VX and the inhibitory potency of the incubate was determined with human acetylcholinesterase (AChE) at 0, 30 and 60 min. In test 2, test materials and nerve agents were mixed and incubated. Between 0 and 40 min samples were taken and incubated for 3 min with AChE and the residual AChE inhibition was determined to enable the semi-quantitative evaluation of the detoxification kinetics. The automated assays proved to be highly reproducible. It was possible to pre-select detoxifying reagents with test 1 and to determine more detailed detoxifying kinetics with test 2.”

The full article can be found at: (T. Wille, et. al., “Development of a high-throughput screening for nerve agent detoxifying materials using a fully-automated robot-assisted biological assay”. Toxicology In Vitro, 2010;24(3):1026-31). Link not available.

ANALYST NOTE: Lead author’s contact information is: Bundeswehr Institute of Pharmacology and Toxicology, Neuherbergstrasse 11, 80937 Munich, Germany.

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A LYOPHILIZED FORMULATION OF RIVAX, A RECOMBINANT RICIN SUBUNIT VACCINE, RETAINS IMMUNOGENICITY
Vaccine Weekly
April 7, 2010

“"Frozen or alum formulations of RiVax protected mice against ricin administered by injection, gavage or aerosol. Without alum, RiVax was safe and immunogenic in rabbits and human volunteers. For military use, the predominant target group, it would be optimal not to require a cold chain for transport and storage.”

"We have now developed a lyophilized formulation and demonstrated stability and efficacy for at least 1 year stored refrigerated or at room temperature administered with or without alum."

The full article can be found at: (J.E. Smallshaw, et. al., "A lyophilized formulation of RiVax, a recombinant ricin subunit vaccine, retains immunogenicity". Vaccine, 2010;28(12):2428-35). Link not available.

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