

6 May 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. UNMASKING ANTHRAX FOR IMMUNE DESTRUCTION: *“Anthrax-causing bacteria can be engineered to shed their invisibility cloaks, making it easier for the immune system to eradicate it, according to a new study published in Microbiology. The work could lead to new measures to treat anthrax infection in the event of a biological warfare attack.”*

2. CHIKUNGUNYA: A POTENTIALLY EMERGING EPIDEMIC?: *“CHIKV mosquito-borne disease has caused massive outbreaks for at least half a century but is no longer confined to the developing nations. It began to encroach into the boundaries of the developing world. As a result, the NIAID has designated CHIKV as a Category C pathogen alongside the influenza and SARS-CoV viruses [3]. Realization of the potential severity of this disease is exigent; for instance, if used as a biological weapon, the world economy could be severely crippled; if enough members of the armed forces were to become infected during a military deployment, military operations could be significantly affected. Efforts to monitor the disease will only provide minimal warning in a global society, and steps to prevent the morbidity and mortality associated with pandemic are imperative.”*

3. RESTRICTING CALORIC INTAKE BOOSTS IMMUNITY: *“Scientists funded by the Agricultural Research Service (ARS) found that volunteers who followed a low-calorie diet or a very low-calorie diet not only lost weight, but also significantly enhanced their immune response. The study may be the first to demonstrate the interaction between calorie restriction and immune markers among humans.”*

4. ISOLATION CRITICAL TO PREVENTING TRANSMISSION OF C. DIFF INFECTION: *“A team of researchers from Leeds Teaching Hospitals National Health Service Trust and the University of Leeds in the United Kingdom is reporting in the latest issue of Clinical Infectious Diseases on the importance of isolation as quickly as possible following the onset of diarrhea to limit the transmission of Clostridium difficile infection (CDI).”*

5. DEADLY CARCINOGEN UNRAVELED: *“When analyzed in light of the biochemical data, these structures revealed for the first time how the region folds an incoming linear carbon chain called a polyketide to form two aflatoxin rings in an amazing feat of origami.”*

6. ANATOMY OF THE EPIDEMIOLOGICAL LITERATURE ON THE 2003 SARS

OUTBREAKS IN HONG KONG AND TORONTO: A TIME-STRATIFIED REVIEW: *“A majority of the epidemiological articles on SARS were submitted after the epidemic had ended, although the corresponding studies had relevance to public health authorities during the epidemic.”*

7. SENSITIVE DETECTION OF MULTIPLEX TOXINS USING ANTIBODY

MICROARRAY: *“In all three cases, polyclonal Abs (pAbs) displayed superiority over monoclonal antibodies (mAbs) in capturing toxins on microarray slides even when the pAbs and mAbs had similar affinity as determined by enzyme-linked immunosorbent assay (ELISA).”*

8. MUTATIONS ABROGATING VP35 INTERACTION WITH DOUBLE-STRANDED RNA

RENDER EBOLA VIRUS AVIRULENT IN GUINEA PIGS: *“These in vivo studies, using recombinant EBOV viruses, combined with the accompanying biochemical and structural analyses directly correlate VP35 dsRNA binding and IFN inhibition functions with viral pathogenesis.”*

9. PITT-LED INTERNATIONAL STUDY IDENTIFIES HUMAN ENZYME THAT BREAKS DOWN POTENTIALLY TOXIC NANOMATERIALS, OPENS DOOR TO NOVEL DRUG

DELIVERY: *“Team of more than 20 researchers directed white blood cells containing the oxidizing enzyme “myeloperoxidase” to attack nanotubes, reducing their unhealthful effects and prompting natural biodegradation, says report in “Nature Nanotechnology”*

10. PROTECTION AGAINST SARIN-INDUCED SEIZURES IN RATS BY DIRECT BRAIN

MICROINJECTION OF SCOPOLAMINE, MIDAZOLAM OR MK-801: *“The results show a unique neuroanatomical and pharmacological specificity for control of nerve agent-induced seizures.”*

CB Daily Report

Chem-Bio News

UNMASKING ANTHRAX FOR IMMUNE DESTRUCTION

Infection Control Today Magazine

May 01, 2010

“Anthrax-causing bacteria can be engineered to shed their invisibility cloaks, making it easier for the immune system to eradicate it, according to a new study published in Microbiology. The work could lead to new measures to treat anthrax infection in the event of a biological warfare attack.

Bacillus anthracis is a particularly lethal pathogen because it manages to escape recognition by the host's immune system by coating itself with a protective capsule around its surface. A key bacterial enzyme called capsule depolymerase (CapD) anchors the capsule to the cell surface. CapD can also cut and release some of the capsule into small fragments that are thought to interfere with specific parts of the immune system, offering further protection to

the bacterium.

Scientists at the U.S. Army Medical Research Institute of Infectious Diseases discovered that by engineering *B. anthracis* to produce higher-than-normal amounts of CapD, the protective capsule is chopped up and released as tiny fragments. The bacterium is left nearly completely unmasked and therefore vulnerable to immediate detection and destruction by the macrophage and neutrophil cells of the immune system. "By engineering *B. anthracis* to over-produce CapD, we are effectively turning the bacterium's own weapon on itself," explained Dr. Arthur Friedlander, one of the principal investigators in the study."

The full article can be found at: <http://www.infectioncontrolday.com/hotnews/unmasking-anthrax-infection.html>

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CHIKUNGUNYA: A POTENTIALLY EMERGING EPIDEMIC?

By Michelle M. Thiboutot, Senthil Kannan, Omkar U. Kawalekar, Devon J. Shedlock, Amir S. Khan, Gopalsamy Sarangan, Padma Srikanth, David B. Weiner, Karupiah Muthumani
PLoS Neglected Tropical Diseases
April 27, 2010

"Abstract Top

Chikungunya virus is a mosquito-borne emerging pathogen that has a major health impact in humans and causes fever disease, headache, rash, nausea, vomiting, myalgia, and arthralgia. Indigenous to tropical Africa, recent large outbreaks have been reported in parts of South East Asia and several of its neighboring islands in 2005–07 and in Europe in 2007. Furthermore, positive cases have been confirmed in the United States in travelers returning from known outbreak areas. Currently, there is no vaccine or antiviral treatment. With the threat of an emerging global pandemic, the peculiar problems associated with the more immediate and seasonal epidemics warrant the development of an effective vaccine. In this review, we summarize the evidence supporting these concepts."

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"Conclusion

CHIKV mosquito-borne disease has caused massive outbreaks for at least half a century but is no longer confined to the developing nations. It began to encroach into the boundaries of the developing world. As a result, the NIAID has designated CHIKV as a Category C pathogen alongside the influenza and SARS-CoV viruses [3]. Realization of the potential severity of this disease is exigent; for instance, if used as a biological weapon, the world economy could be severely crippled; if enough members of the armed forces were to become infected during a military deployment, military operations could be significantly affected. Efforts to monitor the disease will only provide minimal warning in a global society, and steps to prevent the morbidity and mortality associated with pandemic are imperative [21], [31].

Despite the gravity of its infectious potency and the fear of it being a potential biological weapon, there is currently no vaccine for CHIKV infections. Live attenuated vaccine trials were carried out in 2000, but funding for the project was discontinued. Newer approaches such as DNA vaccines appear promising over conventional strategies like live attenuated or inactivated virus and thus call for further investigation. Recent advances such as electroporation delivery and incorporation of adjuvants has boosted DNA vaccine efficacy [51], [53]. Despite the low antibody response to DNA vaccines, other numerous advantages have overshadowed these minor drawbacks (Table 2), the most important one being the ability to induce both humoral and cellular immune responses [51], [54].

Judging by recent success, such as the immunogenic construct developed by Muthumani et al., DNA vaccines could play a major role in combating CHIKV [49]. Vaccines are literally a critical component of CHIKV disease control and therefore research in this area is highly encouraged. The dramatic spread of dengue viruses (DENV) throughout tropical America since 1980 via the same vectors and human hosts underscores the risk to public health in the Americas. The adverse events associated with the current live vaccine are well documented [55]. Realizing these drawbacks, earnest efforts should be taken to develop new strategies to forestall further spread and complications."

The full article can be found at: <http://www.plosntds.org/article/info%3Adoi%2F10.1371%2Fjournal.pntd.0000623;jsessionid=BC592574A45BFBD6CB7241E752CAE1AB>

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RESTRICTING CALORIC INTAKE BOOSTS IMMUNITY

Infection Control Today Magazine

April 29, 2010

"Scientists funded by the Agricultural Research Service (ARS) found that volunteers who followed a low-calorie diet or a very low-calorie diet not only lost weight, but also significantly enhanced their immune response. The study may be the first to demonstrate the interaction between calorie restriction and immune markers among humans.

The lead researcher, Simin Nikbin Meydani, is director of the Jean Mayer USDA Human Nutrition Research Center on Aging (HNRCA) at Tufts University in Boston, and also of the HNRCA's Nutritional Immunology Laboratory.

The study is part of the "Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy" trial conducted at the HNRCA. As people age, their immune response generally declines. Calorie restriction has been shown to boost these immune responses in animal models.

In the study, 46 overweight (but not obese) men and women aged 20 to 40 years were required to consume either a 30 percent or 10 percent calorie-restricted diet for six months.

Prior to being randomly assigned to one of the two groups, each volunteer participated in an

initial six-week period during which measures of all baseline study outcomes were obtained. All food was provided to participants.

For the study, the researchers looked at specific biologic markers. A skin test used called DTH (delayed-type hypersensitivity) is a measure of immune response at the whole body level.

The researchers also examined effects of calorie restriction on function of T-cells -- a major type of white blood cell -- and other factors on the volunteer's immune system.

DTH and T-cell response indicate the strength of cell-mediated immunity. One positive was that DTH and T-cell proliferative response were significantly increased in both calorie-restrained groups.

These results show for the first time that short-term calorie restriction for six months in humans improves the function of T-cells."

The full article can be found at: <http://www.infectioncontrolday.com/hotnews/restricting-caloric-intake-boosts-immunity.html>

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ISOLATION CRITICAL TO PREVENTING TRANSMISSION OF C. DIFF INFECTION

Infection Control Today Magazine

May 02, 2010

"A team of researchers from Leeds Teaching Hospitals National Health Service Trust and the University of Leeds in the United Kingdom is reporting in the latest issue of Clinical Infectious Diseases on the importance of isolation as quickly as possible following the onset of diarrhea to limit the transmission of Clostridium difficile infection (CDI)."

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"The researchers say they conducted air sampling adjacent to 63 CDI patients for 180 total hours and for 101 hours in control settings. Environmental samples were obtained from surfaces adjacent to the patient and from communal areas of the ward. C. difficile isolates were characterized by ribotyping and multi-locus variable number tandem repeat analysis to determine relatedness.

Of the first 50 patients examined (each for one hour), just 12 percent had positive air samples, most frequently those with active symptoms of CDI (10 percent versus 2 percent for those with no symptoms). The researchers intensively sampled the air around 10 patients with CDI symptoms, each for 10 hours over two days, as well as a total of 346 surface sites. C. difficile was isolated from the air in the majority of these cases (7 of 10 patients tested) and from the surfaces around nine of the patients; 60 percent of patients had both air and surface environments that were positive for C. difficile. Molecular

characterization confirmed an epidemiological link between airborne dispersal, environmental contamination, and CDI cases.

The researchers concluded that aerosolization of *C. difficile* occurs commonly but sporadically in patients with symptomatic CDI, thus perhaps explaining the widespread dissemination of epidemic strains. Best, et al. say that their study results emphasize the importance of singleroom isolation as soon as possible after the onset of diarrhea to limit the dissemination of *C. difficile*.

Reference: Best EL, Fawley WN, Parnell P and Wilcox MH. The Potential for Airborne Dispersal of *Clostridium difficile* from Symptomatic Patients. *Clinical Infectious Diseases* 2010; 50: 1450-1457."

The full article can be found at: <http://www.infectioncontroltoday.com/hotnews/isolation-prevents-c-diff-transmission.html>

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DEADLY CARCINOGEN UNRAVELED

Physorg.com

May 04, 2010

"This toxin wreaks havoc on an important gene that prevents cancer. Without the protective effect of this gene, aflatoxin further compromises immunity, interferes with body metabolism, and causes severe malnutrition. It is urgently important to find inexpensive strategies that help protect the world population from aflatoxin food contamination.

A group led by researcher Sheryl Tsai of the University of California at Irvine, in collaboration with the Townsend lab of The Johns Hopkins University, trained SSRL's X-ray beam on a crystallized enzyme in the polyketide synthase family, which is a component of the multi-step process of toxin synthesis. The researchers were able to determine the three-dimensional structures of a region responsible for producing a precursor of the toxin.

When analyzed in light of the biochemical data, these structures revealed for the first time how the region folds an incoming linear carbon chain called a polyketide to form two aflatoxin rings in an amazing feat of origami."

The full article can be found at: <http://www.physorg.com/news192219124.html>

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ANATOMY OF THE EPIDEMIOLOGICAL LITERATURE ON THE 2003 SARS OUTBREAKS IN HONG KONG AND TORONTO: A TIME-STRATIFIED REVIEW

By Weijia Xing, Gilles Hejblum, Gabriel M. Leung, Alain-Jacques Valleron
PLos Medicine

May 04, 2010

"Conclusions

A majority of the epidemiological articles on SARS were submitted after the epidemic had ended, although the corresponding studies had relevance to public health authorities during the epidemic. To minimize the lag between research and the exigency of public health practice in the future, researchers should consider adopting common, predefined protocols and ready-to-use instruments to improve timeliness, and thus, relevance, in addition to standardizing comparability across studies. To facilitate information dissemination, journal managers should reengineer their fast-track channels, which should be adapted to the purpose of an emerging outbreak, taking into account the requirement of high standards of quality for scientific journals and competition with other online resources."

The full article can be found at: <http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000272;jsessionid=AC837F9475C0ACD714941D629D594FF9>

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SENSITIVE DETECTION OF MULTIPLEX TOXINS USING ANTIBODY MICROARRAY

Malaria Weekly

May 10, 2010

"Using a newly developed fluorescent nanoparticle (NP) that gives rise to a high-intensity and stable fluorescent light, a sensitive antibody (Ab) microarray assay system has been developed for specific detection of bioterrorism agents, as exemplified by ricin, cholera toxin (CT), and staphylococcal enterotoxin B (SEB). The Ab microarray uses a sandwich format that consists of capture Abs, analytes (toxins), biotinylated detection Abs, and avidin-conjugated NP."

"In all three cases, polyclonal Abs (pAbs) displayed superiority over monoclonal antibodies (mAbs) in capturing toxins on microarray slides even when the pAbs and mAbs had similar affinity as determined by enzyme-linked immunosorbent assay (ELISA). The detection system was successfully used to detect toxins spiked in milk, apple cider, and blood samples. We were able to detect ricin at 100 pg/ml in buffer and at 1 ng/ml in spiked apple cider or milk, whereas CT and SEB were detected at 10 pg/ml in buffer and 100 pg/ml in spiked apple cider or milk. High specificities were also demonstrated in the detection of mixed toxin samples with similar sensitivities. The matrix effect of blood samples on the detection of mixed toxins seems to be minimal when the toxin concentration is at or above 100 ng/ml."

"The current study highlights the significant role of pAb and NP in increasing selectivity and sensitivity of toxin detection in a microarray format."

The full article can be found at: (W. Lian, et. al., "Sensitive detection of multiplex toxins using antibody microarray". *Analytical Biochemistry*, 2010; 401(2):271-9). Link not available.

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MUTATIONS ABROGATING VP35 INTERACTION WITH DOUBLE-STRANDED RNA RENDER EBOLA VIRUS AVIRULENT IN GUINEA PIGS

Blood Weekly

May 6, 2010

"Ebola virus (EBOV) protein VP35 is a double-stranded RNA (dsRNA) binding inhibitor of host interferon (IFN)-alpha/beta responses that also functions as a viral polymerase cofactor. Recent structural studies identified key features, including a central basic patch, required for VP35 dsRNA binding activity."

"To address the functional significance of these VP35 structural features for EBOV replication and pathogenesis, two point mutations, K319A/R322A, that abrogate VP35 dsRNA binding activity and severely impair its suppression of IFN-alpha/beta production were identified. Solution nuclear magnetic resonance (NMR) spectroscopy and X-ray crystallography reveal minimal structural perturbations in the K319A/R322A VP35 double mutant and suggest that loss of basic charge leads to altered function. Recombinant EBOVs encoding the mutant VP35 exhibit, relative to wild-type VP35 viruses, minimal growth attenuation in IFN-defective Vero cells but severe impairment in IFN-competent cells. In guinea pigs, the VP35 mutant virus revealed a complete loss of virulence. Strikingly, the VP35 mutant virus effectively immunized animals against subsequent wild-type EBOV challenge. These in vivo studies, using recombinant EBOV viruses, combined with the accompanying biochemical and structural analyses directly correlate VP35 dsRNA binding and IFN inhibition functions with viral pathogenesis."

The full article can be found at: (K.C. Prins, et. al., "Mutations Abrogating VP35 Interaction with Double-Stranded RNA Render Ebola Virus Avirulent in Guinea Pigs". Journal of Virology, 2010;84(6):3004-3015). Link not available.

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PITT-LED INTERNATIONAL STUDY IDENTIFIES HUMAN ENZYME THAT BREAKS DOWN POTENTIALLY TOXIC NANOMATERIALS, OPENS DOOR TO NOVEL DRUG DELIVERY

University of Pittsburgh News Release

April 07, 2010

"Team of more than 20 researchers directed white blood cells containing the oxidizing enzyme "myeloperoxidase" to attack nanotubes, reducing their unhealthful effects and prompting natural biodegradation, says report in "Nature Nanotechnology"

"An international study based at the University of Pittsburgh provides the first identification of a human enzyme that can biodegrade carbon nanotubes-the superstrong materials found

in products from electronics to plastics-and in laboratory tests offset the potentially damaging health effects of being exposed to the tiny components, according to findings published online in "Nature Nanotechnology."

The results could open the door to the use of carbon nanotubes as a safe drug-delivery tool and also could lead to the development of a natural treatment for people exposed to nanotubes, either in the environment or the workplace, the team reported. The researchers found that carbon nanotubes degraded with the human enzyme "myeloperoxidase" (hMPO) did not produce the lung inflammation that intact nanotubes have been shown to cause. Furthermore, neutrophils, the white blood cells that contain and emit hMPO to kill invading microorganisms, can be directed to attack carbon nanotubes specifically."

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"For the current study, the researchers focused on human MPO because it works via the release of strong acids and oxidants-similar to the chemicals used to break down carbon nanotubes. They first incubated short, single-walled nanotubes in an hMPO and hydrogen peroxide solution-the hydrogen peroxide sparks and sustains hMPO activity-for 24 hours, after which the structure and bulk of the tube had completely degenerated. The nanotubes degenerated even faster when sodium chloride was added to the solution to produce hypochlorite, a strong oxidizing compound known to break down nanotubes.

After establishing the effectiveness of hMPO in degrading carbon nanotubes, the team developed a technique to prompt neutrophils to attack nanotubes by capturing them and exposing them to the enzyme. They implanted a sample of nanotubes with antibodies known as immunoglobulin G (IgG), which made them specific neutrophil targets. After 12 hours, 100 percent of IgG nanotubes were degraded versus 30 percent of those without IgG. The researchers also tested the ability of macrophages, another white blood cell, to break down nanotubes, but after two days, only 50 percent of the tubes had degenerated.

In subsequent laboratory tests, lung tissue exposed to the degraded nanotubes for seven days exhibited negligible change when compared to unexposed tissue. On the other hand, tissue exposed to untreated nanotubes developed severe inflammation."

The full article can be found at: <http://www.news.pitt.edu/m/FMPro?-db=ma&-lay=a&-format=d.html&id=4037&-Find>

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PROTECTION AGAINST SARIN-INDUCED SEIZURES IN RATS BY DIRECT BRAIN MICROINJECTION OF SCOPOLAMINE, MIDAZOLAM OR MK-801

Pain & Central Nervous System Week

May 10, 2010

"This study began to map the neural areas in rat brain that respond to these three drug classes resulting in anticonvulsant effects. Drugs of each class (scopolamine, midazolam, MK-801) were evaluated for their ability to prevent sarin-induced seizures when injected into

specific brain areas (lateral ventricle, anterior piriform cortex, basolateral amygdala, area tempestas). Animals were pretreated by microinjection with saline or a dose of drug from one of the three classes 30 min prior to receiving 150 microg/kg sarin, subcutaneously, followed by 2.0 mg/kg atropine methylnitrate, intramuscularly. Animals were then returned to their cages, where electroencephalographic activity was monitored for seizures. Anticonvulsant effective doses (ED(50)) were determined using an up-down dosing procedure over successive animals. Scopolamine provided anticonvulsant effects in each area tested, while midazolam was effective in each area except the lateral ventricle. MK-801 was only effective at preventing seizures when injected into the basolateral amygdala or area tempestas."

"The results show a unique neuroanatomical and pharmacological specificity for control of nerve agent-induced seizures."

The full article can be found at: (J.W. Skovira, et. al., "Protection against sarin-induced seizures in rats by direct brain microinjection of scopolamine, midazolam or MK-801". Journal of Molecular Neuroscience, 2010; 40(1-2):56-62). Link not available.

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