18 March 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. CLINICAL AND BIOAVAILABILITY STUDIES OF SUBLINGUALLY ADMINISTERED ATROPINE SULFATE: *"It is a safe and efficacious procedure with the potential to become an alternative to conventional IM injection, particularly in case of chemical terrorism scenario where hundreds of victims may require immediate atropinization simultaneously."*

2. PAPPAIOANOU: VETERINARY CRISIS HAS IMPLICATIONS FOR HUMAN HEALTH: *"With 50 percent of U.S. Public Health Service veterinary medical officers now eligible for retirement, and 43 percent of veterinary pathology positions unfilled, the need for more veterinarians has never been greater."*

3. ALL ABOARD THE DNA NANOTUBE: *"Cargo-carrying DNA nanotubes that can rapidly release their load on demand have been made for the first time by Canadian researchers. The self-assembling nanotubes could help towards the development of biosensing systems or 'nanocapsules' that specifically target diseased cells for drug delivery, the team says."*

4. DEOXYNIVALENOL AND NIVALENOL INHIBIT LIPOPOLYSACCHARIDE-INDUCED NITRIC OXIDE PRODUCTION BY MOUSE MACROPHAGE CELLS: *"These results indicate that DON and NIV inhibit the LPS-induced NO and IFN-beta production, which both play an important role for host protection against invading pathogens, and suggests that the inhibition of these factors may be involved in the immunotoxic effects of these mycotoxins."*

5. MICROFIBRES PURE ENOUGH FOR THE LIVER: *"The liver is one of the most important organs in the human body. It is estimated to have more than 500 functions, including neutralising and destroying drugs and toxins, and converting food into energy. Transplants are the only way to compensate if the liver fails, therefore research is being carried out to develop a method to create artificial 3D liver tissues which can regulate specific functions."*

6. RAPAMYCIN PROTECTS MICE FROM STAPHYLOCOCCAL ENTEROTOXIN B-INDUCED TOXIC SHOCK AND BLOCKS CYTOKINE RELEASE IN VITRO AND IN VIVO: *"In vivo, rapamycin protected 100% of mice from lethal shock, even when administered 24 h after intranasal SEB challenge. The serum levels of MCP-1 and IL-6, after intranasal exposure to SEB, were significantly reduced in mice given rapamycin versus controls."*

7. NOVEL ANTITOXIN STRATEGY DEVELOPED USING 'TAGGED BINDING AGENTS': *"A Tufts-led team developed the new strategy to deliver small binding agents that seek out Botulinum toxin molecules and bind to them at several points."*

8. A BROAD-SPECTRUM ANTIVIRAL TARGETING ENTRY OF ENVELOPED VIRUSES: *"We describe an antiviral small molecule, LJ001, effective against numerous enveloped viruses including Influenza A, filoviruses, poxviruses, arenaviruses, bunyaviruses, paramyxoviruses, flaviviruses, and HIV-1. In sharp contrast, the compound had no effect on the infection of nonenveloped viruses."*

9. TRICHOTHECENES NIV AND DON MODULATE THE MATURATION OF MURINE DENDRITIC CELLS: *"Taken together, our data indicated that the immunotoxicity of NIV and DON was related to the capacity of both trichothecenes to interfere with phenotypic and functional features of maturing DCs."*

10. REGULATION OF MARBURG VIRUS (MARV) BUDDING BY NEDD4.1: A DIFFERENT WW

DOMAIN OF NEDD4.1 IS CRITICAL FOR BINDING TO MARV AND EBOLA VIRUS VP40: *"This is the first report showing that the viral L-domains containing PPxY have specificities for binding to WW domains."*

11. BIOCHEMICAL AND STRUCTURAL CHARACTERIZATION OF CATHEPSIN L-PROCESSED EBOLA VIRUS GLYCOPROTEIN: IMPLICATIONS FOR VIRAL ENTRY AND IMMUNOGENICITY: "*Together, these data suggest that CatL cleavage of EBOV GP exposes its receptor-binding domain, thereby facilitating access to a putative cellular receptor in steps that lead to membrane fusion."*

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CB Daily Report

Chem-Bio News

CLINICAL AND BIOAVAILABILITY STUDIES OF SUBLINGUALLY ADMINISTERED ATROPINE SULFATE
Blood Weekly
March 18, 2010

"The increased use of organophosphorus (OP) pesticides and the ever increasing possibility of terror groups using nerve agents underscore a need to develop effective and safe antidotes against OP poisoning. The objectives of the present study were to develop a novel atropine sulfate (AS) sublingual injection formulation, to create its bioavailability data in humans and to evaluate its suitability for field use with a view to obtain early therapeutic drug concentration in comparison to the conventional intramuscular route that provides a therapeutic peak of 6 to 8 ng/mL in blood at 30 minutes."

"Two milligrams per 0.1 mL of AS was sublingually injected in 6 volunteers, and bioavailability and atropinization signs (blood pressure, pupil diameter, and heart rate) were noted. Human bioavailability curve was created, which was equivalent to 2 mg IM injection in amplitude within 10 minutes and describing a better curve thereafter. Peak plasma concentration of AS occurred at 15 minutes and was 21 ng/mL. Increase in heart rate became extremely significant at 5 minutes ($p < .0001$) with maximum increase of 62% + or -6% at 10 minutes after administration. Pupil diameter showed maximal increase of 58% + or -21% at 15 minutes ($p < .01$). Sublingual AS appears to have several advantages over conventional IM route including better bioavailability, rapid onset of action, and early atropinization."

"It is a safe and efficacious procedure with the potential to become an alternative to conventional IM injection, particularly in case of chemical terrorism scenario where hundreds of victims may require immediate atropinization simultaneously."

The full article can be found at: (S. Rajpal, et. al., "Clinical and bioavailability studies of sublingually administered atropine sulfate". The American Journal of Emergency Medicine, 2010;28(2):143-50). Link not available.
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PAPPAIOANOU: VETERINARY CRISIS HAS IMPLICATIONS FOR HUMAN HEALTH
By Dr. Marguerite Pappaioanou
Roll Call
March 11, 2010

"A perfect storm is approaching, and without Congressional action, the consequences for public health

may be dire.

With 50 percent of U.S. Public Health Service veterinary medical officers now eligible for retirement, and 43 percent of veterinary pathology positions unfilled, the need for more veterinarians has never been greater. But the nation's 28 veterinary medical schools are already at capacity. Applicants outnumber seats by more than 3 to 1. The Bureau of Labor Statistics has projected a need for an additional 22,000 veterinarians by 2016, yet colleges of veterinary medicine have not received direct federal infrastructure support in more than 30 years.

This must change, and it must change soon.

Approximately 61 percent of more than 1,400 infectious disease organisms that cause illness in humans are caused by organisms transmissible from animals to people. Veterinarians have been responsible for some of the most significant advances in public health, including the near eradication of diseases such as tuberculosis and brucellosis in domestic animals."

The full article can be found at: http://www.rollcall.com/news/44112-1.html?mostemailed=1
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ALL ABOARD THE DNA NANOTUBE
By James Urquhart
Chemistry World
March 15, 2010

"Cargo-carrying DNA nanotubes that can rapidly release their load on demand have been made for the first time by Canadian researchers. The self-assembling nanotubes could help towards the development of biosensing systems or 'nanocapsules' that specifically target diseased cells for drug delivery, the team says.

DNA's properties, including chirality and geometry, make it a particularly good construction material for self-assembling nanotubes. Until now, however, no one had figured out how to enclose 'guest' molecules within 3D DNA structures and then release them. But Hanadi Sleiman and Gonzalo Cosa's groups at McGill University in Montreal have now done just that.

'Almost all the DNA construction approaches - such as DNA tiles or DNA origami - reported so far have relied on the use of only DNA to guide the assembly,' says Sleiman. 'In contrast, we incorporate synthetic molecules, such as organic molecules or transition metals, in the junctions of our DNA structures.'

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"To release the cargo, the team added specific strands of DNA that are complementary to the DNA strands that close-in the particles. This causes the nanotubes to become single stranded, thus opening up the capsules and allowing the gold nanoparticles to escape. "

The full article can be found at: http://www.rsc.org/chemistryworld/News/2010/March/15031001.asp
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DEOXYNIVALENOL AND NIVALENOL INHIBIT LIPOPOLYSACCHARIDE-INDUCED NITRIC OXIDE PRODUCTION BY MOUSE MACROPHAGE CELLS
Drug Week
March 19, 2010

"Deoxynivalenol (DON) and nivalenol (NIV), trichothecene mycotoxins, are secondary metabolites

produced by Fusarium fungi. Trichothecene mycotoxins cause immune dysfunction, thus leading to diverse responses to infection."

"The present study evaluated the effect of DON and NIV on nitric oxide (NO) production by RAW264 cells stimulated with lipopolysaccharide (LPS). LPS-induced NO production was reduced in the presence of these toxins. The transcriptional activation and expression of inducible NO synthase (iNOS) by LPS were also repressed by these toxins. DON or NIV inhibited LPS-induced expression of interferon-beta (IFN-beta), which plays an indispensable role in LPS-induced iNOS expression."

"These results indicate that DON and NIV inhibit the LPS-induced NO and IFN-beta production, which both play an important role for host protection against invading pathogens, and suggests that the inhibition of these factors may be involved in the immunotoxic effects of these mycotoxins."

The full article can be found at: (K. Sugiyama, et. al., "Deoxynivalenol and nivalenol inhibit lipopolysaccharide-induced nitric oxide production by mouse macrophage cells". Toxicology Letters, 2010;192(2):150-4). Link not available.
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MICROFIBRES PURE ENOUGH FOR THE LIVER
By Harriet Teare
Highlights in Chemical Biology
March 15, 2010

"A research group in Korea have developed a method to engineer artificial liver tissue using microfluidics.

The liver is one of the most important organs in the human body. It is estimated to have more than 500 functions, including neutralising and destroying drugs and toxins, and converting food into energy. Transplants are the only way to compensate if the liver fails, therefore research is being carried out to develop a method to create artificial 3D liver tissues which can regulate specific functions."

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"Using this method, the team has been able to create a bio-artificial liver chip by culturing HepG2 liver cells on the pure-chitosan fibres. Tests show that vital liver functions including enzyme secretion and urea synthesis were carried out by the cells on the chip, says Lee. This research 'will play a key role to enhance bioartificial liver study,' he adds."

The full article can be found at:
http://www.rsc.org/Publishing/Journals/cb/Volume/2010/04/Microfibres_pure.asp
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RAPAMYCIN PROTECTS MICE FROM STAPHYLOCOCCAL ENTEROTOXIN B-INDUCED TOXIC SHOCK AND BLOCKS CYTOKINE RELEASE IN VITRO AND IN VIVO
Biotech Week
March 24, 2010

"Staphylococcal enterotoxins are potent activators for human T cells and cause lethal toxic shock. Rapamycin, an immunosuppressant, was tested for its ability to inhibit staphylococcal enterotoxin B (SEB)-induced activation of human peripheral blood mononuclear cells (PBMC) in vitro and toxin-mediated shock in mice."

"Stimulation of PMBC by SEB was effectively blocked by rapamycin as evidenced by the inhibition of tumor necrosis factor alpha (TNF-alpha), interleukin 1beta (IL-1beta), IL-6, IL-2, gamma interferon

(IFN-gamma), monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1alpha (MIP-1alpha), MIP-1beta, and T-cell proliferation. In vivo, rapamycin protected 100% of mice from lethal shock, even when administered 24 h after intranasal SEB challenge. The serum levels of MCP-1 and IL-6, after intranasal exposure to SEB, were significantly reduced in mice given rapamycin versus controls."

"Additionally, rapamycin diminished the weight loss and temperature fluctuations elicited by SEB."

The full article can be found at: (T. Krakauer, et. al., "Rapamycin protects mice from staphylococcal enterotoxin B-induced toxic shock and blocks cytokine release in vitro and in vivo". Antimicrobial Agents and Chemotherapy, 2010;54(3):1125-31). Link not available.
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NOVEL ANTITOXIN STRATEGY DEVELOPED USING 'TAGGED BINDING AGENTS'
Tufts University News Release
February 25, 2010

"A Tufts-led team developed the new strategy to deliver small binding agents that seek out Botulinum toxin molecules and bind to them at several points. The binding agents each contain a common "tag" that is recognized by a single, co-administered anti-tag antibody. Once the toxin molecule is surrounded by bound antibodies, it is flushed out of the system through the liver before it can poison the body. Botulinum toxin, which causes botulism, is the most acutely poisonous substance known and is considered among the most dangerous bioterrorist threats. Studies have shown that one gram of the toxin, which is produced by a bacterium that lives in soil, could kill upwards of a million people. Although currently available antitoxins can be mass produced and delivered in the event of an outbreak, they are costly to develop, house and deliver-and have a short shelf-life. The Tufts study, in collaboration with researchers at Thomas Jefferson University in Philadelphia, is published this month in the journal Infection and Immunity and was funded by the National Institutes of Allergy and Infectious Diseases (NIAID) and the New England Regional Center for Excellence (NERCE) for Biodefense and Emerging Infectious Diseases.

"We've proven this approach to protect against Botulinum intoxication in mice and we hope this will lead to rapid development and deployment of many new anti-toxin therapies-for botulism and beyond," said Charles B. Shoemaker, PhD, professor of biomedical sciences at Tufts University's Cummings School of Veterinary Medicine and the study's corresponding author."

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"Instead of using three antibodies, the Tufts approach uses three small binding agents to direct a single monoclonal antibody to multiple sites on the biomolecule being targeted for clearance. The type of binding agents used can be selected from many scaffolds developed for commercial therapeutic applications (e.g. nanobodies, aptamers, darpins, FN3, microbodies, etc). These binding agents can be rapidly identified and improved using modern technologies and generally have excellent commercial production and product shelf-life properties. The single anti-tag monoclonal antibody can also be selected to have optimal isotype and commercialization properties.

What's more, the binding agents can be produced with more than one tag, which enables them to direct more antibodies to the toxin—and synergistically improve target clearance from the body. Many binding agent scaffolds can be produced as functional multimers so that the different binding agents could be produced as "beads on a string," leading to a single molecule that targets one, or even several, biomolecules for clearance from the body.

Using this approach, the researchers say, one would only need to create new binding agents, not new antibodies, to create a therapy to clear a toxin from the body—paving the way for new therapies that combat toxins ranging from animal venom to bioterrorist agents such as ricin. Tufts researchers are

currently targeting Shiga toxin and C. difficile along with other types of Botulinum toxin. Future plans include targeting clearance of pathogenic cytokines that are implicated in inflammation and autoimmune diseases."

The full article can be found at: http://news.tufts.edu/releases/release.php?id=156
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A BROAD-SPECTRUM ANTIVIRAL TARGETING ENTRY OF ENVELOPED VIRUSES
Preventive Medicine Week
March 21, 2010

"We describe an antiviral small molecule, LJ001, effective against numerous enveloped viruses including Influenza A, filoviruses, poxviruses, arenaviruses, bunyaviruses, paramyxoviruses, flaviviruses, and HIV-1. In sharp contrast, the compound had no effect on the infection of nonenveloped viruses."

"In vitro and in vivo assays showed no overt toxicity. LJ001 specifically intercalated into viral membranes, irreversibly inactivated virions while leaving functionally intact envelope proteins, and inhibited viral entry at a step after virus binding but before virus-cell fusion. LJ001 pretreatment also prevented virus-induced mortality from Ebola and Rift Valley fever viruses. Structure-activity relationship analyses of LJ001, a rhodanine derivative, implicated both the polar and nonpolar ends of LJ001 in its antiviral activity. LJ001 specifically inhibited virus-cell but not cell-cell fusion, and further studies with lipid biosynthesis inhibitors indicated that LJ001 exploits the therapeutic window that exists between static viral membranes and biogenic cellular membranes with reparative capacity."

"In sum, our data reveal a class of broad-spectrum antivirals effective against enveloped viruses that target the viral lipid membrane and compromises its ability to mediate virus-cell fusion."

The full article can be found at: (M.C. Wolfe, et. al., "A broad-spectrum antiviral targeting entry of enveloped viruses". Proceedings of the National Academy of Sciences of the United States of America, 2010;107(7):3157-62). Link not available.
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TRICHOTHECENES NIV AND DON MODULATE THE MATURATION OF MURINE DENDRITIC CELLS
Energy & Ecology
March 19, 2010

"Murine bone marrow-derived DCs were used to evaluate the effects of NIV and DON on the LPS-induced maturation process. We found that the expression of the class 11 MHC and of the accessory CD11c molecules, but not of the costimulatory CD86 marker, was down-regulated by NIV and DON exposure in LPS-treated DCs, as well as nitric oxide (NO) production. Interestingly, NIV, but not DON, induced DC necrosis. Moreover, the analysis of the cytokine pattern showed that IL-12 and IL-10 expressions induced by LPS exposure were suppressed by both trichothecenes in a dose-dependent fashion. on the other hand, the secretion of the proinflammatory cytokine TNF-alpha was increased as a direct consequence of DON and NIV exposure."

"Taken together, our data indicated that the immunotoxicity of NIV and DON was related to the capacity of both trichothecenes to interfere with phenotypic and functional features of maturing DCs."

The full article can be found at: (D. Luongo, et. al., "Trichothecenes NIV and DON modulate the maturation of murine dendritic cells". Toxicon, 2010;55(1):73-80). Link not available.
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REGULATION OF MARBURG VIRUS (MARV) BUDDING BY NEDD4.1: A DIFFERENT WW DOMAIN OF NEDD4.1 IS CRITICAL FOR BINDING TO MARV AND EBOLA VIRUS VP40
Hematology Week
March 15, 2010

"The VP40 matrix protein of Marburg virus (MARV) has been shown to be the driving force behind MARV budding, a process in which the PPPY L-domain motif of VP40 plays a critical role. Here, we report that Vps4B and Nedd4.1 play critical roles in MARV VP40-mediated budding, We showed that unidentified activities of the Nedd4.1 HECT domain, along with its E3 ubiquitin ligase activity, may be required for MARV budding."

"Moreover, we showed that the first WW domain of Nedd4.1, WW1, is critical for binding to MARV VP40, indicating that MARV VP40 and Ebola virus VP40 are recognized by a different WW domain of Nedd4.1. This is the first report showing that the viral L-domains containing PPxY have specificities for binding to WW domains."

The full article can be found at: (S. Urata, et. al., "Regulation of Marburg virus (MARV) budding by Nedd4.1: a different WW domain of Nedd4.1 is critical for binding to MARV and Ebola virus VP40". Journal of General Virology, 2010;91(Part 1):228-234). Link not available.
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BIOCHEMICAL AND STRUCTURAL CHARACTERIZATION OF CATHEPSIN L-PROCESSED EBOLA VIRUS GLYCOPROTEIN: IMPLICATIONS FOR VIRAL ENTRY AND IMMUNOGENICITY
Immunotherapy Weekly
March 24, 2010

"Ebola virus (EBOV) cellular attachment and entry is initiated by the envelope glycoprotein (GP) on the virion surface. Entry of this virus is pH dependent and associated with the cleavage of GP by proteases, including cathepsin L (CatL) and/or CatB, in the endosome or cell membrane."

"Here, we characterize the product of CatL cleavage of Zaire EBOV GP (ZEBOV-GP) and evaluate its relevance to entry. A stabilized recombinant form of the EBOV GP trimer was generated using a trimerization domain linked to a cleavable histidine tag. This trimer was purified to homogeneity and cleaved with CatL. Characterization of the trimeric product by N-terminal sequencing and mass spectrometry revealed three cleavage fragments, with masses of 23, 19, and 4 kDa. Structure-assisted modeling of the cathepsin L-cleaved ZEBOV-GP revealed that cleavage removes a glycosylated glycan cap and mucin-like domain (MUC domain) and exposes the conserved core residues implicated in receptor binding. The CatL-cleaved ZEBOV-GP intermediate bound with high affinity to a neutralizing antibody, KZ52, and also elicited neutralizing antibodies, supporting the notion that the processed intermediate is required for viral entry."

"Together, these data suggest that CatL cleavage of EBOV GP exposes its receptor-binding domain, thereby facilitating access to a putative cellular receptor in steps that lead to membrane fusion."

The full article can be found at: (C.L. Hood, et. al., "Biochemical and structural characterization of cathepsin L-processed ebola virus glycoprotein: implications for viral entry and immunogenicity". Journal of Virology, 2010;84(6):2972-82). Link not available.
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CHARACTERIZATION OF TWO PROLINE DIPEPTIDASES (PROLIDASES) FROM THE HYPERTHERMOPHILIC ARCHAEON PYROCOCCUS HORIKOSHII
Proteomics Weekly
March 15, 2010

Prolidases hydrolyze the unique bond between X-Pro dipeptides and can also cleave the P-F and P-O

bonds found in organophosphorus compounds, including the nerve agents, soman and sarin. The advantages of using hyperthermophilic enzymes in biodetoxification strategies are based on their enzyme stability and efficiency."

"Therefore, it is advantageous to examine new thermostable prolidases for potential use in biotechnological applications. Two thermostable prolidase homologs, PH1149 and PH0974, were identified in the genome of Pyrococcus horikoshii based on their sequences having conserved metal binding and catalytic amino acid residues that are present in other known prolidases, such as the previously characterized Pyrococcus furiosus prolidase. These P. horikoshii prolidases were expressed recombinantly in the Escherichia coli strain BL21 (lambda DE3), and both were shown to function as proline dipeptidases. Biochemical characterization of these prolidases shows they have higher catalytic activities over a broader pH range, higher affinity for metal and are more stable compared to P. furiosus prolidase."

"This study has important implications for the potential use of these enzymes in biotechnological applications and provides further information on the functional traits of hyperthermophilic proteins, specifically metalloenzymes."

The full article can be found at: (C.M. Theriot, et. al., "Characterization of two proline dipeptidases (Prolidases) from the hyperthermophilic archaeon Pyrococcus horikoshii". Applied Microbiology and Biotechnology, 2010;86(1):177-188). Link not available.
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