

4 September 2008

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 Supplement

1. NEW ETHANOL-BASED HAND SANITIZER MAY MINIMIZE VIRAL TRANSMISSION, INCLUDING NOROVIRUS:

"When compared with a benchmark alcohol-based hand sanitizer, results showed higher levels of reduced infectivity of human rotavirus, adenovirus type 5, poliovirus type 1, and norovirus, as well as feline calicivirus and murine norovirus type 1 from the new ethanol-based sanitizer."

2. DRUG DISCOVERY ON A CHIP: *"Scientists in the US have, for the first time, used microfluidics to discover drug leads. The team's lab-on-a-chip device revealed inhibitors of a key membrane-bound protein in hepatitis C virus (HCV)."*

3. PHOSPHOINOSITIDE-3 KINASE-AKT [PI3K-AKT] PATHWAY CONTROLS

CELLULAR ENTRY OF EBOLA VIRUS: *"We conclude that PI3K-mediated signaling plays an important role in regulating vesicular trafficking of ZEBOV[Zaire Ebola virus] necessary for cell entry."*

4. ZAK: A MAP3KINASE THAT TRANSDUCES SHIGA TOXIN- AND RICIN-INDUCED PROINFLAMMATORY CYTOKINE EXPRESSION:

"Furthermore, a small molecule inhibitor like DHP-2 may prove valuable in preventing the Stx/ricin-induced proinflammatory and/or apoptotic effects that are thought to contribute to pathogenesis by Stx-producing Escherichia coli and ricin."

5. DEVELOPMENT OF AN AUTOMATED ON-LINE PEPSIN DIGESTION-LIQUID CHROMATOGRAPHY-TANDEM MASS SPECTROMETRY CONFIGURATION FOR THE

RAPID ANALYSIS OF PROTEIN ADDUCTS OF CHEMICAL WARFARE AGENTS: *"The utility of this configuration is demonstrated by the analysis of specific adducts of sarin and sulfur mustard to human butyryl cholinesterase and human serum albumin, respectively."*

6. UNSYMMETRIC ARYL-ALKYL DISULFIDE GROWTH INHIBITORS OF METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS [MRSA] AND BACILLUS ANTHRACIS:

"These structurally simple disulfides have been found to inhibit beta-ketoacyl-acyl carrier protein synthase III, or FabH, a key enzyme in type II fatty acid biosynthesis, and thus may serve as new leads to the development of effective antibacterials for MRSA and anthrax infections."

7. DOUBLE EMULSIONS COULD CARRY COMBINATION THERAPIES: *“Timothy Deming and colleagues at the University of California, Los Angeles, have created the first double emulsions to contain droplets just 10 to 100 nanometres in diameter - in the range required to ferry drugs into cells.”*

CB Daily Report

Chem-Bio News

NEW ETHANOL-BASED HAND SANITIZER MAY MINIMIZE VIRAL TRANSMISSION, INCLUDING NOROVIRUS

Infection Control Today Magazine
August 26, 2008

“A newly developed ethanol-based hand sanitizer may significantly impact public health by minimizing the transmission of multiple viruses, including norovirus, from food handlers and healthcare providers. The researchers from the University of Ottawa, Ontario, Canada, and North Carolina State University, Raleigh report their findings in the August 2008 issue of the journal Applied and Environmental Microbiology.”

“In the study the researchers formed a synergistic blend of ethanol, polyquaternium polymer and organic acid and tested its capability to inhibit human and animal viruses. When compared with a benchmark alcohol-based hand sanitizer, results showed higher levels of reduced infectivity of human rotavirus, adenovirus type 5, poliovirus type 1, and norovirus, as well as feline calicivirus and murine norovirus type 1 from the new ethanol-based sanitizer.”

The full article can be found at: <http://www.infectioncontrolday.com/hotnews/hand-sanitizer-viral-transmission-norovirus.html>

The original article can be found at: D.R. Macinga, S.A. Sattar, L. Jaykus, J.W. Arbogast. 2008. Improved inactivation of nonenveloped enteric viruses and their surrogates by a novel alcohol-based hand sanitizer. Applied and Environmental Microbiology, 74. 16: 5047-5052. Link not available.

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DRUG DISCOVERY ON A CHIP

By James Mitchell Crow
Chemistry World
September 1, 2008

“Scientists in the US have, for the first time, used microfluidics to discover drug leads. The team's lab-on-a-chip device revealed inhibitors of a key membrane-bound protein in hepatitis C virus (HCV).”

Stephen Quake, Jeffrey Glenn and colleagues at Stanford University investigated a protein called NS4B - which plays an essential role in the virus's ability to cause infection - as a potential drug target. The team first used their microfluidic device to confirm that NS4B binds RNA as the virus replicates. They then screened a library of 1280 small molecules to identify inhibitors of this protein-RNA interaction."

"But Glenn and his team devised a way to make just enough of the protein to be tested. 'We've found that if you synthesise NS4B in vitro with microsomal membranes, we provide the conditions for it to fold properly - but the problem is that this process yields only small amounts of the protein,' he says. 'We were lucky to have Stephen Quake across the hall - a world expert with a technique ideally suited to studying small amounts of protein.'

Having used microfluidics to confirm NS4B's role in binding RNA, the team decided to take the process one step further and use it to screen for small molecule inhibitors - the first time the technology had been used to screen for drug leads. 'One of the hits - clemizole - is very potent in vivo, with significant antiviral activity and no toxicity, and has been used in humans before,' adds Glenn. The team plan to use the device to further optimise the compound, and also to investigate a variety of other potential HCV targets."

The full article can be found at: <http://www.rsc.org/chemistryworld/News/2008/September/01090802.asp>

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PHOSPHOINOSITIDE-3 KINASE-AKT [PI3K-AKT] PATHWAY CONTROLS CELLULAR ENTRY OF EBOLA VIRUS

By Mohammad F. Saeed, Andrey A. Kolokoltssov, Alexander N. Freiberg, Michael R. Holbrook, Robert A. Davey
PLoS Pathogens
September 2, 2008

"Here, the involvement of PI3K in Ebola virus entry was studied. A novel and critical role of the PI3K signaling pathway was demonstrated in cell entry of Zaire Ebola virus (ZEBOV). Inhibitors of PI3K and Akt significantly reduced infection by ZEBOV at an early step during the replication cycle. Furthermore, phosphorylation of Akt-1 was induced shortly after exposure of cells to radiation-inactivated ZEBOV, indicating that the virus actively induces the PI3K pathway and that replication was not required for this induction. Subsequent use of pseudotyped Ebola virus and/or Ebola virus-like particles, in a novel virus entry assay, provided evidence that activity of PI3K/Akt is required at the virus entry step. Class 1A PI3Ks appear to play a predominant role in regulating ZEBOV entry, and Rac1 is a key downstream effector in this regulatory cascade. Confocal imaging of fluorescently labeled ZEBOV indicated that inhibition of PI3K, Akt, or Rac1 disrupted normal uptake of virus particles into cells and resulted in aberrant accumulation of virus into a cytosolic compartment that was non-permissive for membrane fusion. We conclude that PI3K-mediated signaling plays an important role in regulating vesicular trafficking of ZEBOV

necessary for cell entry. Disruption of this signaling leads to inappropriate trafficking within the cell and a block in steps leading to membrane fusion. These findings extend our current understanding of Ebola virus entry mechanism and may help in devising useful new strategies for treatment of Ebola virus infection."

The full article can be found at: <http://www.plospathogens.org/article/info%3Adoi%2F10.1371%2Fjournal.ppat.1000141>

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ZAK: A MAP3KINASE THAT TRANSDUCES SHIGA TOXIN- AND RICIN-INDUCED PROINFLAMMATORY CYTOKINE EXPRESSION

Preventive Medicine Week

September 7, 2008

"Shiga toxins (Stxs) and ricin initiate damage to host cells by cleaving a single adenine residue on the alpha-sarcin loop of the 28S ribosomal RNA. This molecular insult results in a cascade of intracellular events termed the ribotoxic stress response (RSR)."

"Although Stxs and ricin have been shown to cause the RSR, the mitogen-activated protein kinase kinase kinase (MAP3K) that transduces the signal from intoxicated ribosomes to activate SAPKinases has remained elusive. We show in vitro that DHP-2 (7-[3-fluoro-4-aminophenyl-(4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl))]-quinoline), a zipper sterile-alpha-motif kinase (ZAK)-specific inhibitor, blocks Stx2/ricin-induced SAPKinase activation. Treatment of cells with DHP-2 also blocks Stx2/ricin-mediated upregulation of the proinflammatory cytokine interleukin-8 and results in a modest but statistically significant improvement in cell viability following Stx2/ricin treatment. Finally we show that siRNA directed against the N-terminus of ZAK diminishes Stx2/Ricin-induced SAPKinase activation. Together, these data demonstrate that a ZAK isoform(s) is the MAP3Kinase that transduces the RSR. Therefore, ZAK alpha and/or beta isoforms may act as potential therapeutic target(s) for treating Stx/ricin-associated illnesses."

"Furthermore, a small molecule inhibitor like DHP-2 may prove valuable in preventing the Stx/ricin-induced proinflammatory and/or apoptotic effects that are thought to contribute to pathogenesis by Stx-producing Escherichia coli and ricin."

The full article can be found at: (D.M. Jandhyala, et. al., "ZAK: a MAP3Kinase that transduces Shiga toxin- and ricin-induced proinflammatory cytokine expression". Cellular Microbiology, 2008; 10(7):1468-1477). Link not available.

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DEVELOPMENT OF AN AUTOMATED ON-LINE PEPSIN DIGESTION-LIQUID CHROMATOGRAPHY-TANDEM MASS SPECTROMETRY CONFIGURATION FOR THE RAPID ANALYSIS OF PROTEIN ADDUCTS OF CHEMICAL WARFARE AGENTS

Medical Letter on the CDC & FDA
September 7, 2008

"Liquid chromatography-mass spectrometry (LC-MS) is the tool of choice in the analysis of such protein adducts, but the overall experimental procedure is quite elaborate. Therefore, an automated on-line pepsin digestion-LC-MS configuration has been developed for the rapid determination of CWA protein adducts."

"The utility of this configuration is demonstrated by the analysis of specific adducts of sarin and sulfur mustard to human butyryl cholinesterase and human serum albumin, respectively."

The full article can be found at: (J. Carol-Visser, et. al., "Development of an automated on-line pepsin digestion-liquid chromatography-tandem mass spectrometry configuration for the rapid analysis of protein adducts of chemical warfare agents". *Journal of Chromatography B*, 2008; 870(1):91-7). Link not available.

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UNSYMMETRIC ARYL-ALKYL DISULFIDE GROWTH INHIBITORS OF METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS [MRSA] AND BACILLUS ANTHRACIS

Drug Week

September 5, 2008

"Our results indicate that among the 12 different aryl substituents examined, nitrophenyl derivatives provide the strongest antibiotic activities. This may be the result of electronic activation of the arylthio moiety as a leaving group for nucleophilic attack on the disulfide bond. Small alkyl residues on the other sulfur provide the best activity as well, which for different bacteria appears to be somewhat dependent on the nature of the alkyl moiety. The mechanism of action of these lipophilic disulfides is likely similar to that of previously reported N-thiolated beta-lactams, which have been shown to produce alkyl-CoA disulfides through a thiol-disulfide exchange within the cytoplasm, ultimately inhibiting type II fatty acid synthesis. However, the mixed alkyl-CoA disulfides themselves show no antibacterial activity, presumably due to the inability of the highly polar compounds to cross the bacterial cell membrane."

"These structurally simple disulfides have been found to inhibit beta-ketoacyl-acyl carrier protein synthase III, or FabH, a key enzyme in type II fatty acid biosynthesis, and thus may serve as new leads to the development of effective antibacterials for MRSA and anthrax infections."

The full article can be found at: (E. Turos, et. al., "Unsymmetric aryl-alkyl disulfide growth inhibitors of methicillin-resistant *Staphylococcus aureus* and *Bacillus anthracis*". *Bioorganic & Medicinal Chemistry*, 2008; 16(13):6501-6508). Link not available.

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DOUBLE EMULSIONS COULD CARRY COMBINATION THERAPIES

By Hayley Birch

Chemistry World

September 3, 2008

"US scientists have made nanoscale water-in-oil-in-water (WOW) emulsions that could have important applications in drug delivery.

Timothy Deming and colleagues at the University of California, Los Angeles, have created the first double emulsions to contain droplets just 10 to 100 nanometres in diameter - in the range required to ferry drugs into cells. Crucially, a stable mixture of oil and water droplets would allow drug designers to combine polar and non-polar therapeutic molecules in a single treatment.

The researchers are able to form their nanoscale emulsions, and keep them stable for months at a time, by adding copolypeptide surfactants. These surfactants - long chain molecules, polar at one end and non-polar at the other - straddle the oil-water interface, and are designed to make the oil layer harder to breach from the inside, says Deming. 'So the inner droplets are trapped - they can't get out to the bulk phase,' he adds.

The key feature of these surfactants is that their hydrophobic end, which sits in the oil layer, is made from a mixture of L- and R-amino acid enantiomers. This makes their 3D structures more irregular and frees up hydrogen bonding groups that would otherwise be involved in keeping each molecule wound in a tight helix."

The full article can be found at: <http://www.rsc.org/chemistryworld/News/2008/September/03090801.asp>

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