

5 November 2009

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. A COMPARISON OF THE REACTIVATING AND THERAPEUTIC EFFICACY OF NEWLY DEVELOPED BISPYRIDINIUM OXIMES (K250, K251) WITH COMMONLY USED OXIMES AGAINST TABUN IN RATS AND MICE:

“Thus, the reactivating and therapeutic potency of both newly developed oximes (K250, K251) does not prevail over the effectiveness of currently available oximes and, therefore, they are not suitable for their replacement for the treatment of acute tabun poisoning.”

2. SMALL MOLECULE CONTROL OF VIRULENCE GENE EXPRESSION IN FRANCISELLA TULARENSIS:

*“Here we show that in the intracellular pathogen *F. tularensis*, ppGpp plays a critical role in controlling the expression of genes required for intracellular replication and virulence, and we uncover the molecular basis for its effect. In particular, we show that ppGpp works in concert with three other essential regulators of virulence gene expression in *F. tularensis*—a putative DNA-binding protein that we have called PigR and the SspA protein family members MglA and SspA.”*

3. NEW WAY TO FIND DRUGS' UNINTENDED TARGETS: *“The exhaustive survey yielded hundreds of previously unrecognized possible interactions between drugs and protein receptors in the body. A number of these were confirmed by experiments in the laboratory, including the identification of the key receptor that binds the hallucinatory drug dimethyltryptamine - something that has been hotly debated recently.”*

4. REDUCED LEVELS OF PROTEIN TYROSINE PHOSPHATASE CD45 PROTECT MICE FROM THE LETHAL EFFECTS OF EBOLA VIRUS INFECTION:

“Together, these findings suggest that host susceptibility to EBOV is dependent on the delicate balance of immune homeostasis, which, as demonstrated here, can be determined by the levels of a single regulator.”

5. A NEUTRALIZING HUMAN MONOCLONAL ANTIBODY PROTECTS AGAINST LETHAL DISEASE IN A NEW FERRET MODEL OF ACUTE NIPAH VIRUS INFECTION:

“All ferrets that received m102.4 ten hours following a high dose oral-nasal Nipah virus challenge were protected from disease while all controls died. This study is the first successful post-exposure passive antibody therapy for Nipah virus using a human monoclonal antibody.”

6. ANALGESIC EFFECT FROM IBUPROFEN NANOPARTICLES INHALED BY MALE

MICE: *"Aerosol lung administration is a convenient way to deliver water-insoluble or poorly soluble drugs, provided that small-sized particles are generated. Here, for the outbred male mice, we show that the pulmonary administration of ibuprofen nanoparticles requires a dose that is three to five orders of magnitude less than that for the orally delivered particles at the same analgesic effect."*

7. STICKY POLYMERS FOR WOUND HEALING: *"Temperature-responsive gels are showing promise for tissue regeneration therapy, according to researchers in the UK."*

CB Daily Report

Chem-Bio News

A COMPARISON OF THE REACTIVATING AND THERAPEUTIC EFFICACY OF NEWLY DEVELOPED BISPYRIDINIUM OXIMES (K250, K251) WITH COMMONLY USED OXIMES AGAINST TABUN IN RATS AND MICE

Drug Week

November 6, 2009

"The potency of newly developed bispyridinium compounds (K250, K251) in reactivating tabun-inhibited acetylcholinesterase and reducing tabun-induced lethal toxic effects was compared with currently available oximes (obidoxime, trimedoxime, the oxime HI-6) using in vivo methods. Studies determined percentage of reactivation of tabun-inhibited blood and tissue AChE in poisoned rats and showed that the reactivating efficacy of both newly developed oximes is comparable with the oxime HI-6 but it is significantly lower than the reactivating effects of obidoxime and trimedoxime, especially in diaphragm and brain."

"Both newly developed oximes were also found to be able to slightly reduce lethal toxic effects in tabun-poisoned mice. Their therapeutic efficacy is higher than the potency of the oxime HI-6 but it is lower than the therapeutic effects of trimedoxime and obidoxime."

"Thus, the reactivating and therapeutic potency of both newly developed oximes (K250, K251) does not prevail over the effectiveness of currently available oximes and, therefore, they are not suitable for their replacement for the treatment of acute tabun poisoning."

The full article can be found at: (J. Kassa, et. al., "A comparison of the reactivating and therapeutic efficacy of newly developed bispyridinium oximes (K250, K251) with commonly used oximes against tabun in rats and mice". Journal of Enzyme Inhibition and Medicinal Chemistry, 2009; 24(4): 1040-1044). Link not available.

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SMALL MOLECULE CONTROL OF VIRULENCE GENE EXPRESSION IN FRANCISELLA TULARENSIS

By James C. Charity, LeeAnn T. Blalock, Michelle M. Costante-Hamm, Dennis L. Kasper, Simon L. Dove
PLoS Pathogens
October 30, 2009

“Abstract

In *Francisella tularensis*, the SspA protein family members MglA and SspA form a complex that associates with RNA polymerase (RNAP) to positively control the expression of virulence genes critical for the intramacrophage growth and survival of the organism. Although the association of the MglA-SspA complex with RNAP is evidently central to its role in controlling gene expression, the molecular details of how MglA and SspA exert their effects are not known. Here we show that in the live vaccine strain of *F. tularensis* (LVS), the MglA-SspA complex works in concert with a putative DNA-binding protein we have called PigR, together with the alarmone guanosine tetraphosphate (ppGpp), to regulate the expression of target genes. In particular, we present evidence that MglA, SspA, PigR and ppGpp regulate expression of the same set of genes, and show that *mglA*, *sspA*, *pigR* and *ppGpp* null mutants exhibit similar intramacrophage growth defects and are strongly attenuated for virulence in mice. We show further that PigR interacts directly with the MglA-SspA complex, suggesting that the central role of the MglA and SspA proteins in the control of virulence gene expression is to serve as a target for a transcription activator. Finally, we present evidence that ppGpp exerts its effects by promoting the interaction between PigR and the RNAP-associated MglA-SspA complex. Through its responsiveness to ppGpp, the contact between PigR and the MglA-SspA complex allows the integration of nutritional cues into the regulatory network governing virulence gene expression.

Author Summary

Guanosine tetraphosphate (ppGpp) is a small molecule that is produced by many different bacteria in response to nutrient limitation. Although ppGpp has been shown to play an important role in controlling the expression of virulence genes in several pathogenic bacteria, few studies have addressed how this occurs. Here we show that in the intracellular pathogen *F. tularensis*, ppGpp plays a critical role in controlling the expression of genes required for intracellular replication and virulence, and we uncover the molecular basis for its effect. In particular, we show that ppGpp works in concert with three other essential regulators of virulence gene expression in *F. tularensis*—a putative DNA-binding protein that we have called PigR and the SspA protein family members MglA and SspA. Our study provides evidence that ppGpp functions to promote the interaction between PigR and a component of *F. tularensis* RNA polymerase (RNAP) comprising the MglA and SspA proteins. By influencing the interaction between PigR and the RNAP-associated MglA-SspA complex, ppGpp serves to tie the nutritional status of the cell to the expression of genes that are essential for survival in the host.”

The full article can be found at: <http://www.plospathogens.org/article/info%3Adoi%2F10.1371%2Fjournal.ppat.1000641;jsessionid=2D7E85390B90391A18833D91CC6DC118>

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NEW WAY TO FIND DRUGS' UNINTENDED TARGETS

By Simon Hadlington
Chemistry World
November 02, 2009

"Identifying these off-target effects has proved difficult, time-consuming and costly. Now, a team led by Brian Shoichet of the University of California San Francisco has combined powerful computational, statistical and experimental techniques to predict off-target interactions.

On one side the researchers lined up 3,665 existing and experimental drugs. On the other side they assembled over 65,000 known ligands to protein receptors in the body, arranging the ligands into around 250 classes depending on the type of receptor they bind to. They then used chemoinformatics and statistical programs to identify similarities between the drugs and the set of known ligands.

'We define ligands by their topologies - atoms, functional groups, and the bonds between them,' says Shoichet. 'There are subtle features whose importance only appears on considering the full set, or a large part of it, of the known ligands. Hence the focus on comparing drugs to the full 'ensemble' of the known ligands.' A second important nuance, Shoichet goes on to explain, is that all comparisons are corrected for the similarity one would expect at random. 'This allows us to give statistical weights on the similarities we would observe. This is essentially new to the field of making chemical comparisons, though it is widely used in biology - from where we stole it.'

The exhaustive survey yielded hundreds of previously unrecognised possible interactions between drugs and protein receptors in the body. A number of these were confirmed by experiments in the laboratory, including the identification of the key receptor that binds the hallucinatory drug dimethyltryptamine - something that has been hotly debated recently."

The full article can be found at: <http://www.rsc.org/chemistryworld/News/2009/November/02110901.asp>

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REDUCED LEVELS OF PROTEIN TYROSINE PHOSPHATASE CD45 PROTECT MICE FROM THE LETHAL EFFECTS OF EBOLA VIRUS INFECTION

Blood Weekly
October 29, 2009

"Although rodents are resistant to EBOV, a murine-adapted variant is lethal when injected intraperitoneally into mice. We find that mice expressing reduced levels of the tyrosine

phosphatase CD45 are protected against EBOV, whereas wild-type, CD45-deficient, or enzymatically inactive CD45-expressing mice succumbed to infection. Protection was dependent on CD8(+) T cells and interferon gamma. Reduced CD45-expressing mice retained greater control of gene expression and immune cell proliferation following EBOV infection, which contributed to reduced apoptosis, enhanced viral clearance, and increased protection against the virus."

"Together, these findings suggest that host susceptibility to EBOV is dependent on the delicate balance of immune homeostasis, which, as demonstrated here, can be determined by the levels of a single regulator."

The full article can be found at: (R.G. Panchal, et. al., "Reduced Levels of Protein Tyrosine Phosphatase CD45 Protect Mice from the Lethal Effects of Ebola Virus Infection". *Cell Host & Microbe*, 2009;6(2):162-173). Link not available.

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A NEUTRALIZING HUMAN MONOCLONAL ANTIBODY PROTECTS AGAINST LETHAL DISEASE IN A NEW FERRET MODEL OF ACUTE NIPAH VIRUS INFECTION

By Katharine N. Bossart, Zhongyu Zhu, Deborah Middleton, Jessica Klippel, Gary Cramer¹, John Bingham, Jennifer A. McEachern, Diane Green, Timothy J. Hancock, Yee-Peng Chan, Andrew C. Hickey, Dimiter S. Dimitrov, Lin-Fa Wang, Christopher C. Broder

PLoS Pathogens

October 30, 2009

"Abstract

Nipah virus is a broadly tropic and highly pathogenic zoonotic paramyxovirus in the genus Henipavirus whose natural reservoirs are several species of Pteropus fruit bats. Nipah virus has repeatedly caused outbreaks over the past decade associated with a severe and often fatal disease in humans and animals. Here, a new ferret model of Nipah virus pathogenesis is described where both respiratory and neurological disease are present in infected animals. Severe disease occurs with viral doses as low as 500 TCID₅₀ within 6 to 10 days following infection. The underlying pathology seen in the ferret closely resembles that seen in Nipah virus infected humans, characterized as a widespread multisystemic vasculitis, with virus replicating in highly vascular tissues including lung, spleen and brain, with recoverable virus from a variety of tissues. Using this ferret model a cross-reactive neutralizing human monoclonal antibody, m102.4, targeting the henipavirus G glycoprotein was evaluated in vivo as a potential therapeutic agent. All ferrets that received m102.4 ten hours following a high dose oral-nasal Nipah virus challenge were protected from disease while all controls died. This study is the first successful post-exposure passive antibody therapy for Nipah virus using a human monoclonal antibody.

Author Summary

Nipah virus and Hendra virus are closely related and highly pathogenic zoonoses whose primary natural reservoirs are several species of Pteropus fruit bats. Both Nipah and Hendra

viruses can cause severe and often fatal disease in a variety of mammalian hosts, including humans. The henipaviruses are categorized as biosafety level 4 (BSL-4) agents, which has limited the development of animal models and the testing of potential therapeutics and vaccine countermeasures. We show here a new ferret model of Nipah virus pathogenesis in which the underlying pathology closely mirrors the illness seen in Nipah virus-infected humans, including both respiratory and neurological disease. We also show that m102.4, a cross-reactive neutralizing human monoclonal antibody that targets the viral attachment glycoprotein, completely protected ferrets from disease when given ten hours after a lethal Nipah virus challenge. This study is the first successful and viable post-exposure passive antibody therapy for Nipah virus using a human monoclonal antibody."

The full article can be found at: <http://www.plospathogens.org/article/info%3Adoi%2F10.1371%2Fjournal.ppat.1000642;jsessionid=13F9B9CB2D571D1B47733A3805C180D8>

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ANALGESIC EFFECT FROM IBUPROFEN NANOPARTICLES INHALED BY MALE MICE

Drug Week

October 30, 2009

"Aerosol lung administration is a convenient way to deliver water-insoluble or poorly soluble drugs, provided that small-sized particles are generated. Here, for the outbred male mice, we show that the pulmonary administration of ibuprofen nanoparticles requires a dose that is three to five orders of magnitude less than that for the orally delivered particles at the same analgesic effect."

"The aerosol evaporation-condensation generator consisted of a horizontal cylindrical quartz tube with an outer heater. Argon flow was supplied to the inlet and aerosol was formed at the outlet. The particle mean diameter and number concentration varied from 10 to 100 nm and $10(3) - 10(7) \text{ cm}^{-3}$, respectively. The analgesic action and side pulmonary effects caused by the inhalation of ibuprofen nanoparticles were investigated. The chemical composition of aerosol particles was shown to be identical with the maternal drug. Using the nose-only exposure chambers, the mice lung deposition efficiency was evaluated as a function of the particle diameter. The dose-dependent analgesic effect of aerosolized ibuprofen was studied in comparison with the oral treatment. It was found that the dose for aerosol treatment is three to five orders of magnitude less than that required for oral treatment at the same analgesic effect."

"Accompanying effects were moderate venous hyperemia and some emphysematous signs."

The full article can be found at: (A.A. Onischuk, et. al., "Analgesic Effect from Ibuprofen Nanoparticles Inhaled by Male Mice". *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2009; 22(3): 245-253). Link not available.

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STICKY POLYMERS FOR WOUND HEALING

By Michael Spencelayh

Highlights in Chemical Biology

October 23, 2009

"Temperature-responsive gels are showing promise for tissue regeneration therapy, according to researchers in the UK.

Stephen Rimmer of the University of Sheffield and colleagues have modified a water-swollen polymer gel with a cell-adhesive peptide. The gel can be used to pick up skin cells and move them to a new substrate, where they can then be gently detached. Rimmer explains that a motivation for the team was the gel's potential applications in wound healing, as the second substrate could potentially be a damaged tissue. 'Cell therapy for regenerating tissues requires transporting the cells to the desired wound bed,' he says.

Rimmer's gel works by binding to surface proteins on cells grown in a normal culture, thus removing them from the substrate. In the next step, cooling the swollen gel from the 37°C cell culture temperature to below 34°C causes it to swell even further, which has the effect of reducing cell adhesion. This releases the bound cells and can be used to deposit them at a new location."

The full article can be found at: http://www.rsc.org/Publishing/Journals/cb/Volume/2009/12/sticky_polymers.asp

The original article can be found at: Sub-micron poly(N-isopropylacrylamide) particles as temperature responsive vehicles for the detachment and delivery of human cells, Sally Hopkins, Steven R. Carter, John W. Haycock, Nigel J. Fullwood, Sheila MacNeil and Stephen Rimmer, *Soft Matter*, 2009, DOI: 10.1039/b909656f

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