

29 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. HUMAN CARBOXYLESTERASE 1 STEREOSELECTIVELY BINDS THE NERVE AGENT CYCLOSARIN AND SPONTANEOUSLY HYDROLYZES THE NERVE AGENT SARIN:** *"These results provide important insights toward the long-term goal of designing novel forms of hCE1 to act as protein-based therapeutics for nerve agent detoxification."*
- 2. POPULATION GENETIC ANALYSES OF FUSARIUM ASIATICUM POPULATIONS FROM BARLEY SUGGEST A RECENT SHIFT FAVORING 3ADON PRODUCERS IN SOUTHERN CHINA:** *"Using Bayesian statistics, we found a biased gene flow from 3ADON to nivalenol (NIV) Populations. In addition, we observed significant genetic differentiation and linkage disequilibrium between NIV- and 3ADON-producing isolates at the same sampling sites."*
- 3. SYNTHESIS AND BIOLOGICAL EVALUATION OF BOTULINUM NEUROTOXIN A PROTEASE INHIBITORS:** *"Structure-activity relationship studies have revealed structural features important to potency and enzyme specificity."*
- 4. INFRARED DIFFERENTIAL-ABSORPTION MUELLER MATRIX SPECTROSCOPY AND NEURAL NETWORK-BASED DATA FUSION FOR BIOLOGICAL AEROSOL STANDOFF DETECTION:** *"A typical ANN that mathematically clusters analyte, interferent, and control aerosols with nil overlap of species is illustrated, including sensitivity analysis of performance."*
- 5. ION-MOLECULE REACTIONS OF O,S-DIMETHYL METHYLPHOSPHONOTHIOATE: EVIDENCE FOR INTRAMOLECULAR SULFUR OXIDATION DURING VX PERHYDROLYSIS:** *"Elimination of a sulfur moiety deactivates the nerve agent VX and thus the intramolecular sulfur oxidation process reported here is also able to explain the selective perhydrolysis of the nerve agent to relatively nontoxic products."*
- 6. SULFONATED POLYANILINE NETWORK GRAFTED MULTI-WALL CARBON NANOTUBES FOR ENZYME IMMOBILIZATION, DIRECT ELECTROCHEMISTRY AND BIOSENSING OF GLUCOSE:** *"At a low applied potential of -0.1 V. MWNT-g-SPAN-NW/GOx electrode possesses high sensitivity (4.34 $\mu\text{A mM}^{-1}$) and reproducibility towards glucose."*
- 7. BIOSENSOR SYSTEM-ON-A-CHIP INCLUDING CMOS-BASED SIGNAL PROCESSING CIRCUITS AND 64 CARBON NANOTUBE-BASED SENSORS FOR THE DETECTION OF A NEUROTRANSMITTER:** *"This is a major technological advancement in the integration of CNT-based sensors with microelectronics, and this chip can be readily integrated with larger scale lab-on-a-chip (LoC) systems for various applications such as LoC systems for neural networks."*
- 8. LESS IS MORE! NANOPATCH IS 100 TIMES BETTER THAN NEEDLE AND SYRINGE:** *"New research, led by Professor Mark Kendall, from UQ's Australian Institute for Bioengineering and Nanotechnology, demonstrates that a vaccine delivered by a Nanopatch induces a similarly protective immune response as a vaccine delivered by needle and syringe, but uses 100 times less vaccine."*
- 9. NOVEL NANOPARTICLES PREVENT RADIATION DAMAGE:** *"Tiny, melanin-covered nanoparticles may protect bone marrow from the harmful effects of radiation therapy, according to scientists at Albert Einstein College of Medicine of Yeshiva University who successfully tested the strategy in mouse models. Infusing these particles into human patients may hold promise in the future. The research is described in the current issue of the International Journal of Radiation Oncology, Biology and Physics."*
- 10. RICIN ANTIDOTE ON THE HORIZON:** *"For the first time, compounds that protect against ricin*

poisoning have been identified by French researchers. It's hoped the research could lead to an antidote for the poison, which is a thousand times more toxic than cyanide."

11. SMART DRUG DELIVERY VIA THERMO-TRIGGERED SQUIRTING: "Nanoparticles are becoming more widespread for disease diagnosis and therapy but protecting them from degradation and delivering them to target tissue is still a challenge. Some promising drug delivery systems exhibit low physical and chemical stabilities causing them to leak or deliver the nanoparticles too early. Now Liang-Yin Chu and colleagues, from Sichuan University, have developed hydrogel capsules that protect the nanoparticles, and release them only in response to a change in temperature."

CB Daily Report

Chem-Bio News

HUMAN CARBOXYLESTERASE 1 STEREOSELECTIVELY BINDS THE NERVE AGENT CYCLOSARIN AND SPONTANEOUSLY HYDROLYZES THE NERVE AGENT SARIN

Drug Week
April 30, 2010

"The drug-metabolizing enzyme human carboxylesterase 1 (hCE1) is a candidate protein-based therapeutic because of its similarity in structure and function to the cholinesterase targets of nerve agent poisoning. However, the ability of wild-type hCE1 to process the G-type nerve agents sarin and cyclosarin has not been determined. We report the crystal structure of hCE1 in complex with the nerve agent cyclosarin. We further use stereoselective nerve agent analogs to establish that hCE1 exhibits a 1700- and 2900-fold preference for the P® enantiomers of analogs of soman and cyclosarin, respectively, and a 5-fold preference for the P(S) isomer of a sarin analog. Finally, we show that for enzyme inhibited by racemic mixtures of bona fide nerve agents, hCE1 spontaneously reactivates in the presence of sarin but not soman or cyclosarin. The addition of the neutral oxime 2,3-butanedione monoxime increases the rate of reactivation of hCE1 from sarin inhibition by more than 60-fold but has no effect on reactivation with the other agents examined. Taken together, these data demonstrate that hCE1 is only reactivated after inhibition with the more toxic P(S) isomer of sarin."

"These results provide important insights toward the long-term goal of designing novel forms of hCE1 to act as protein-based therapeutics for nerve agent detoxification."

The full article can be found at: (A.C. Hemmert, et. al., "Human carboxylesterase 1 stereoselectively binds the nerve agent cyclosarin and spontaneously hydrolyzes the nerve agent sarin". *Molecular Pharmacology*, 2010;77(4):508-16). Link not available.

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POPULATION GENETIC ANALYSES OF FUSARIUM ASIATICUM POPULATIONS FROM BARLEY SUGGEST A RECENT SHIFT FAVORING 3ADON PRODUCERS IN SOUTHERN CHINA

Agriculture Business Week
April 29, 2010

"Fusarium asiaticum is the predominant causal agent of Fusarium head blight (FHB) in southern China. The genetic diversity was assessed by analyzing 448 single-spore F. asiaticum isolates from 18 sampling sites that were 10 to 2,000 km apart, using seven highly informative variable number of tandem repeat (VNTR) markers."

"This analysis showed a significant degree of population subdivision ($P < 0.001$) among populations from upper, middle, and lower valleys of the Yangtze River, with little gene flow ($N_m = 1.210$). We observed a strong association between this genetic Population subdivision and the mycotoxin produced. Our results show that the dramatic cline in trichothecene chemotypes may be explained by a recent and significant invasion of 3-acetyldeoxynivalenol (3ADON) producers in FHB pathogen composition in the

middle valley. Using Bayesian statistics, we found a biased gene flow from 3ADON to nivalenol (NIV) Populations. In addition, we observed significant genetic differentiation and linkage disequilibrium between NIV- and 3ADON-producing isolates at the same sampling sites."

The full article can be found at: (H. Zhang, et. al., "Population Genetic Analyses of Fusarium asiaticum Populations from Barley Suggest a Recent Shift Favoring 3ADON Producers in Southern China". *Phytopathology*, 2010;100(4):328-336). Link not available.

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SYNTHESIS AND BIOLOGICAL EVALUATION OF BOTULINUM NEUROTOXIN A PROTEASE INHIBITORS

Cancer Weekly
April 20, 2010

"NSC 240898 was previously identified as a botulinum neurotoxin A light chain (BoNT/A LC) endopeptidase inhibitor by screening the National Cancer Institute Open Repository diversity set. Two types of analogues have been synthesized and shown to inhibit BoNT/A LC in a FRET-based enzyme assay, with confirmation in an HPLC-based assay."

"These two series of compounds have also been evaluated for inhibition of anthrax lethal factor (LF), an unrelated metalloprotease, to examine enzyme specificity of the BoNT/A LC inhibition. The most potent inhibitor against BoNT/A LC in these two series is compound 12 (IC(50)=2.5 microM, FRET assay), which is 4.4-fold more potent than the lead structure and 11.2-fold more selective for BoNT/A LC versus the anthrax LF metalloproteinase."

"Structure-activity relationship studies have revealed structural features important to potency and enzyme specificity."

The full article can be found at: (B. Li, et. al., "Synthesis and biological evaluation of botulinum neurotoxin a protease inhibitors". *Journal of Medicinal Chemistry*, 2010;53(5):2264-76). Link not available.

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INFRARED DIFFERENTIAL-ABSORPTION MUELLER MATRIX SPECTROSCOPY AND NEURAL NETWORK-BASED DATA FUSION FOR BIOLOGICAL AEROSOL STANDOFF DETECTION

Health & Medicine Week
April 19, 2010

"An active spectrophotopolarimeter sensor and support system were developed for a military/civilian defense feasibility study concerning the identification and standoff detection of biological aerosols. Plumes of warfare agent surrogates gamma-irradiated *Bacillus subtilis* and chicken egg white albumen (analytes), Arizona road dust (terrestrial interferent), water mist (atmospheric interferent), and talcum powders (experiment controls) were dispersed inside windowless chambers and interrogated by multiple CO(2) laser beams spanning 9.1-12.0 microm wavelengths (λ)."

"Molecular vibration and vibration-rotation activities by the subject analyte are fundamentally strong within this 'fingerprint' middle infrared spectral region. Distinct polarization-modulations of incident irradiance and backscatter radiance of tuned beams generate the Mueller matrix (M) of subject aerosol. Strings of all 15 normalized elements $\{M(ij)(\lambda)/M(11)(\lambda)\}$, which completely describe physical and geometric attributes of the aerosol particles, are input fields for training hybrid Kohonen self-organizing map feed-forward artificial neural networks (ANNs). The properly trained and validated ANN model performs pattern recognition and type-classification tasks via internal mappings."

"A typical ANN that mathematically clusters analyte, interferent, and control aerosols with nil overlap of species is illustrated, including sensitivity analysis of performance."

The full article can be found at: (A.H. Carrieri, et. al., "Infrared differential-absorption Mueller matrix spectroscopy and neural network-based data fusion for biological aerosol standoff detection". Applied Optics, 2010;49(3):382-93). Link not available.

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ION-MOLECULE REACTIONS OF O,S-DIMETHYL METHYLPHOSPHONOTHIOATE: EVIDENCE FOR INTRAMOLECULAR SULFUR OXIDATION DURING VX PERHYDROLYSIS

Drug Week

April 23, 2010

"The alkaline perhydrolysis of the nerve agent O-ethyl S-[2-(diisopropylamino)ethyl] methylphosphonothioate (VX) was investigated by studying the ion-molecule reactions of HOO(-) with O,S-dimethyl methylphosphonothioate in a modified linear ion-trap mass spectrometer. In addition to simple proton transfer, two other abundant product ions are observed at m/z 125 and 109 corresponding to the S-methyl methylphosphonothioate and methyl methylphosphonate anions, respectively."

"The structure of these product ions is demonstrated by a combination of collision-induced dissociation and isotope-labeling experiments that also provide evidence for their formation by nucleophilic reaction pathways, namely, (i) S(N)2 at carbon to yield the S-methyl methylphosphonothioate anion and (ii) nucleophilic addition at phosphorus affording a reactive pentavalent intermediate that readily undergoes internal sulfur oxidation and concomitant elimination of CH(3)SOH to yield the methyl methylphosphonate anion. Consistent with previous solution phase observations of VX perhydrolysis, the toxic P-O cleavage product is not observed in this VX model system and theoretical calculations identify P-O cleavage to be energetically uncompetitive. Conversely, intramolecular sulfur oxidation is calculated to be extremely exothermic and kinetically accessible explaining its competitiveness with the facile gas phase proton transfer process."

"Elimination of a sulfur moiety deactivates the nerve agent VX and thus the intramolecular sulfur oxidation process reported here is also able to explain the selective perhydrolysis of the nerve agent to relatively nontoxic products."

The full article can be found at: (A.M. McAnoy, et. al., "Ion-molecule reactions of O,S-dimethyl methylphosphonothioate: evidence for intramolecular sulfur oxidation during VX perhydrolysis". Journal of Organic Chemistry, 2009;74(24):9319-27). Link not available.

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SULFONATED POLYANILINE NETWORK GRAFTED MULTI-WALL CARBON NANOTUBES FOR ENZYME IMMOBILIZATION, DIRECT ELECTROCHEMISTRY AND BIOSENSING OF GLUCOSE

Journal of Technology & Science

May 2, 2010

"A new nanomaterial was prepared by grafting a layer of sulfonated polyaniline network (SPAN-NW) on to the surface of multi-walled carbon nanotube (MWNT) and effectively utilized for immobilization of an enzyme and for the fabrication of a biosensor. SPAN-NW was formed on the surface of MWNT by polymerizing a mixture of diphenyl amine 4-sulfonic acid (DPASA), 4-vinyl aniline (VA) and 2-acrylamido-2-methyl-1-propane sulfonic acid (APASA) in the presence of amine functionalized MWNT (MWNT-NH2)."

"The MWNT-g-SPAN-NW was immobilized with glucose oxidase (GOx) to fabricate the SPAN-NW/GOx biosensor. MWNT-g-SPAN-NW/GOx electrode showed direct electron transfer (DET) for GOx with a fast heterogeneous electron transfer rate constant (k(s)) of 4.11 s(-1). The amperometric current response of MWNT-g-SPAN-NW/ GOx biosensor shows linearity up to 9 mM of glucose, with a correlation coefficient of 0.99 and a detection limit of 0.11 mc M (S/N = 3)."

The full article can be found at: (K.P. Lee, et. al., "Sulfonated polyaniline network grafted multi-wall carbon nanotubes for enzyme immobilization, direct electrochemistry and biosensing of glucose". Microchemical Journal, 2010;95(1 Sp. Iss.):74-79). Link not available.

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BIOSENSOR SYSTEM-ON-A-CHIP INCLUDING CMOS-BASED SIGNAL PROCESSING CIRCUITS AND 64 CARBON NANOTUBE-BASED SENSORS FOR THE DETECTION OF A NEUROTRANSMITTER

Journal of Technology & Science

May 2, 2010

"We developed a carbon nanotube (CNT)-based biosensor system-on-a-chip (SoC) for the detection of a neurotransmitter."

"Here, 64 CNT-based sensors were integrated with silicon-based signal processing circuits in a single chip, which was made possible by combining several technological breakthroughs such as efficient signal processing, uniform CNT networks, and biocompatible functionalization of CNT-based sensors. The chip was utilized to detect glutamate, a neurotransmitter, where ammonia, a byproduct of the enzymatic reaction of glutamate and glutamate oxidase on CNT-based sensors, modulated the conductance signals to the CNT-based sensors."

"This is a major technological advancement in the integration of CNT-based sensors with microelectronics, and this chip can be readily integrated with larger scale lab-on-a-chip (LoC) systems for various applications such as LoC systems for neural networks."

The full article can be found at: (B.Y. Lee, et. al., "Biosensor system-on-a-chip including CMOS-based signal processing circuits and 64 carbon nanotube-based sensors for the detection of a neurotransmitter". Lab on a Chip, 2010;10(7):894-898). Link not available.

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LESS IS MORE! NANOPATCH IS 100 TIMES BETTER THAN NEEDLE AND SYRINGE

Nanotechwire.com

April 22, 2010

"New research, led by Professor Mark Kendall, from UQ's Australian Institute for Bioengineering and Nanotechnology, demonstrates that a vaccine delivered by a Nanopatch induces a similarly protective immune response as a vaccine delivered by needle and syringe, but uses 100 times less vaccine.

This discovery has implications for many vaccination programs in both industrialised and developing nations, which must overcome issues with vaccine shortages and distribution.

Being both painless and needle-free, the nanopatch offers hope for those with needle phobia, as well as improving the vaccination experience for young children.

"The Nanopatch targeted specific antigen-presenting cells found in a narrow layer just beneath the skin surface and as a result we used less than one hundredth of the dose used by a needle while stimulating a comparable immune response," Professor Kendall said.

"Our result is ten times better than the best results achieved by other delivery methods and does not require the use of other immune stimulants, called adjuvants, or multiple vaccinations.

"Because the Nanopatch requires neither a trained practitioner to administer it nor refrigeration, it has enormous potential cheaply deliver vaccines in developing nations," he said.

Professor Kendall said the Nanopatch was much smaller than a postage stamp and comprised of several thousands of densely packed projections invisible to the human eye.

The influenza vaccine was dry coated onto these projections and applied to the skin of mice for two minutes. "By using far less vaccine we believe that the Nanopatch will enable the vaccination of many

more people," Professor Kendall said.

"When compared to a needle and syringe a nanopatch is cheap to produce and it is easy to imagine a situation in which a government might provide vaccinations for a pandemic such as swine flu to be collected from a chemist or sent in the mail."

The full article can be found at: <http://nanotechwire.com/news.asp?nid=9770>

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NOVEL NANOPARTICLES PREVENT RADIATION DAMAGE

Nanotechwire.com

April 28, 2010

"Tiny, melanin-covered nanoparticles may protect bone marrow from the harmful effects of radiation therapy, according to scientists at Albert Einstein College of Medicine of Yeshiva University who successfully tested the strategy in mouse models. Infusing these particles into human patients may hold promise in the future. The research is described in the current issue of the International Journal of Radiation Oncology, Biology and Physics."

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"A technique for shielding normal cells from radiation damage would allow doctors to administer higher doses of radiation to tumors, making the treatment more effective," said Ekaterina Dadachova, Ph.D., associate professor of nuclear medicine and of microbiology & immunology and the Sylvia and Robert S. Olnick Faculty Scholar in Cancer Research at Einstein, as well as senior author of the study.

In previously published research, Dr. Dadachova and colleagues showed that melanin protects against radiation by helping prevent the formation of free radicals, which cause DNA damage, and by scavenging the free radicals that do form.

"We wanted to devise a way to provide protective melanin to the bone marrow," said Dr. Dadachova. "That's where blood is formed, and the bone-marrow stem cells that produce blood cells are extremely susceptible to the damaging effects of radiation."

Dr. Dadachova and her colleagues focused on packaging melanin in particles so small that they would not get trapped by the lungs, liver or spleen. They created "melanin nanoparticles" by coating tiny (20 nanometers in diameter) silica (sand) particles with several layers of melanin pigment that they synthesized in their laboratory.

The researchers found that these particles successfully lodged in bone marrow after being injected into mice. Then, in a series of experiments, they investigated whether their nanoparticles would protect the bone marrow of mice treated with two types of radiation."

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"Some nanoparticles could still be found in bone marrow 24 hours after their injection, which shouldn't pose a problem. "Since the nanoparticles are rapidly removed by phagocytic cells, they're unlikely to damage the bone marrow," said Dr. Dadachova. "We didn't detect any side effects associated with administering the particles."

"These results are encouraging for other potential applications of melanin, including radioprotection of other radiation-sensitive tissues, such as the gastrointestinal tract," noted Andrew Schweitzer, M.D., formerly a Howard Hughes Medical Institute fellow at Einstein and lead author of the study."

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“The paper, “Melanin-covered nanoparticles for protection of bone marrow during radiation therapy of cancer,” was published in the April 26 online issue of the International Journal of Radiation Oncology, Biology and Physics. Other researchers involved in the study are Ekaterina Revskaya, Ph.D., Peter Chu, B.Sc., Matthew Friedman, Joshua D. Nosanchuk, M.D., Sean Cahill, Ph.D., and Susana Frases, Ph.D., all from Einstein, and Valeria Pazo, M.D., of Jacobi Medical Center.”

The full article can be found at: <http://nanotechwire.com/news.asp?nid=9807>

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RICIN ANTIDOTE ON THE HORIZON

By Lewis Brindley

Chemistry World

April 23, 2010

“For the first time, compounds that protect against ricin poisoning have been identified by French researchers. It's hoped the research could lead to an antidote for the poison, which is a thousand times more toxic than cyanide.”

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“Research has been undertaken into an antibody-based vaccine and antidote at the Defence Science and Technology Laboratory in Porton Down, Wiltshire, UK, but they are not yet widely available.

There is currently no antidote for ricin intoxication,' says Daniel Gillet, who led the project at the biological research division of the French Atomic Energy and Alternative Energies Commission (CEA). In collaboration with Ludger Johannes at the Curie Institute in Paris, the team screened 16,480 different compounds to search for any that offered protection. Of these, two were found to protect mice from being killed by a lethal dose of ricin - and were surprisingly low in toxicity themselves.....”

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“Retro-1 and Retro-2 may also find roles in fighting virulent bacterial toxins (called Shiga toxins) that attack cells with a similar mechanism, Hay adds. 'Significantly, the effectiveness of these two compounds might treat other toxin-related illnesses such as that caused by cholera or E.coli because their toxins follow a similar route to the ribosome,' he says.”

The full article can be found at: <http://www.rsc.org/chemistryworld/News/2010/April/23041001.asp>

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SMART DRUG DELIVERY VIA THERMO-TRIGGERED SQUIRTING

By Jon Watson

Highlights in Chemical Science

April 27, 2010

“Nanoparticles are becoming more widespread for disease diagnosis and therapy but protecting them from degradation and delivering them to target tissue is still a challenge. Some promising drug delivery systems exhibit low physical and chemical stabilities causing them to leak or deliver the nanoparticles too early. Now Liang-Yin Chu and colleagues, from Sichuan University, have developed hydrogel capsules that protect the nanoparticles, and release them only in response to a change in temperature.

Chu encapsulated the nanoparticles in a water/oil emulsion inside a NIPAM-based hydrogel. Heating the capsules above a critical temperature triggers rapid shrinkage, which increases the internal pressure. Because the hydrogels have a low mechanical strength, the capsule violently ruptures, squirting the

nanoparticles out. Chu says the inspiration for these nanoparticles bombs came from plants, such as the squirting cucumber (*ecballium elaterium*), that eject their seeds into the air by sudden contraction of their walls.

The key to the site-specific delivery is the use of a remote trigger (temperature) to tune exactly when and where the capsules rupture. This allows the release of the drug at exactly the right time and place. Crucially, Chu has been able to tune the temperature at which this squirting happens to above body temperature, so the capsules can be used in the body. Local thermotherapy at the target site, using microwave, ultrasound or infrared irradiation could be used to trigger the nanoparticle release.”

The full article can be found at:

http://www.rsc.org/Publishing/ChemScience/Volume/2010/06/smart_drug_delivery.asp

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