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Chem-Bio News – S&T Edition

1. DEGRADATION OF SULFUR MUSTARD AND SARIN OVER HARDENED CEMENT PASTE: *"The molecules of GB adsorbed over HCP in comparison with HD could be more quickly and completely degraded into hydrolyzed products such as isopropyl methylphosphonic acid and methylphosphonic acid by adsorbed water, in comparison with HD."*

2. RAPID DETERMINATION OF HYDROGEN POSITIONS AND PROTONATION STATES OF DIISOPROPYL FLUOROPHOSPHATASE BY JOINT NEUTRON AND X-RAY DIFFRACTION REFINEMENT: *"The extended network of hydrogen bonding interactions in the central water filled tunnel of DFPase is revealed, showing that internal solvent molecules form an important, integrated part of the overall structure."*

3. GAO SAYS HUMAN EXPERIMENTATION SYSTEM 'VULNERABLE TO UNETHICAL MANIPULATION': *"To test the human-trials authorization system, the GAO investigators "created a Web site for a bogus IRB and advertised the bogus IRB's services in newspapers and online."*

4. TOTAL SYNTHESIS OF (-)- AND (+)-DECARBAMOYLOXYSAXITOXIN AND (+)-SAXITOXIN: *"This approach provides efficient access to the key diamine intermediate for STXs."*

5. BUTYRYLCHOLINESTERASE: BIOMARKER FOR EXPOSURE TO ORGANOPHOSPHORUS INSECTICIDES: *"Despite the complexities of their interpretation, BuChE measurements remain a mainstay for the fast initial screening of exposure to OP; thus, they are a useful tool in the protection of humans, domestic animals and wildlife from overexposure to these toxic agents."*

6. PREDICTION OF GAS CHROMATOGRAPHIC RETENTION INDICES OF ORGANOPHOSPHORUS COMPOUNDS BY HOLOGRAPHIC QSRR [QUANTITATIVE STRUCTURE-RETENTION RELATIONSHIP]: *"A new molecular structure representation, molecular hologram, is employed to investigate the quantitative relationship between gas chromatographic retention indices and molecular structures for 41 methyl-esterified organophosphorus compounds (OPs)."*

7. ANTHRAX PROTECTIVE ANTIGEN DELIVERED BY SALMONELLA ENTERICA SEROVAR TYPHI TY21A PROTECTS MICE FROM A LETHAL ANTHRAX SPORE CHALLENGE: *"The ultimate goal is a temperature-stable, safe, oral human vaccine against anthrax infection that can be self-administered in a few doses over a short period of time."*

8. CHARACTERIZATION OF VIBRIO CHOLERAЕ OUTER MEMBRANE VESICLES AS A CANDIDATE VACCINE FOR CHOLERA: *"The detection of an immune response against this heterologously expressed protein is a promising step toward the potential use of OMVs as antigen delivery vehicles in vaccine design."*

9. CHIP MIMICS METABOLISM: *"Drug metabolism studies can be conducted on smaller samples than before thanks to an on-chip electrochemical cell designed by European scientists."*

CB Daily Report

Chem-Bio News

DEGRADATION OF SULFUR MUSTARD AND SARIN OVER HARDENED CEMENT PASTE

Ecology, Environment & Conservation

April 3, 2009

"A study has been done to examine the degradation of sulfur mustard (HD) and Sarin (GB) over hardened cement paste (HCP). The HCP behaved as a typical base like CaO and Ca(OH)₂, The base sites over the HCP were not entirely poisoned by H₂O and CO₂ in air, and about 0.47 mmol/g base sites could still be evidenced by chemisorption of CO₂."

"A large amount of water irreversibly adsorbed by HCP was experimentally demonstrated. Ten kinds of products through hydrolysis S(N)₁ (C-Cl), elimination E-1 or E-2 (C-Cl, C-H), and addition-elimination (A-E) under the action of base sites and water from the degradation of HD over HCP were detected and identified by GC-FPD, GC-MS, and NMR approaches. Their distribution and kinds varied with time of degradation and water content. Both degradation activity and distribution of products from HD were strongly determined by the strength and density of base sites and the water content in HCP."

"The molecules of GB adsorbed over HCP in comparison with HD could be more quickly and completely degraded into hydrolyzed products such as isopropyl methylphosphonic acid and methylphosphonic acid by adsorbed water, in comparison with HD."

The full article can be found at: (H.R. Tang, et. al., "Degradation of Sulfur Mustard and Sarin over Hardened Cement Paste". Environmental Science & Technology, 2009;43(5):1553-1558). Link not available.

Analyst Note: The study's POC is listed as: Z.X. Cheng, Institute Chemical Def, Dept. of 3, POB 1048, Beijing 102205, People's Republic of China.

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RAPID DETERMINATION OF HYDROGEN POSITIONS AND PROTONATION STATES OF DIISOPROPYL FLUOROPHOSPHATASE BY JOINT NEUTRON AND X-RAY DIFFRACTION REFINEMENT

Proteomics Weekly

March 30, 2009

"Hydrogen atoms constitute about half of all atoms in proteins and play a critical role in enzyme mechanisms and macromolecular and solvent structure. Hydrogen atom positions can readily be determined by neutron diffraction, and as such, neutron diffraction is an invaluable tool for elucidating molecular mechanisms."

"Joint refinement of neutron and X-ray diffraction data can lead to improved models compared with the use of neutron data alone and has now been incorporated into modern, maximum-likelihood based crystallographic refinement programs like CNS. Joint refinement has been applied to neutron and X-ray diffraction data collected on crystals of diisopropyl fluorophosphatase (DFPase), a calcium-dependent phosphotriesterase capable of detoxifying organophosphorus nerve agents. Neutron omit maps reveal a number of important features pertaining to the mechanism of DFPase. Solvent molecule W33, coordinating the catalytic calcium, is a water molecule in a strained coordination environment, and not a hydroxide. The smallest Ca-O-H angle is 53 degrees, well beyond the smallest angles previously observed. Residue Asp-229, is deprotonated, supporting a mechanism involving nucleophilic attack by Asp-229, and excluding water activation by the catalytic calcium."

"The extended network of hydrogen bonding interactions in the central water filled tunnel of DFPase is revealed, showing that internal solvent molecules form an important, integrated part of the overall structure."

The full article can be found at: (M.M. Bluma, et. al., "Rapid determination of hydrogen positions and protonation states of diisopropyl fluorophosphatase by joint neutron and X-ray diffraction refinement". Proceedings of the National Academy of Sciences of the United States of America, 2009;106(3):713-

718). Link not available.

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GAO SAYS HUMAN EXPERIMENTATION SYSTEM 'VULNERABLE TO UNETHICAL MANIPULATION'

By Louis Chunovic

Government Security News

March 27, 2009

"In theory, independent institutional review boards (IRBs) review and monitor human subjects research, with a mandate to protect the rights and welfare of the research subjects. Those IRBs are, in turn, supposedly monitored by the Department of Health and Human Services' (HHS) Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA).

To test the human-trials authorization system, the GAO investigators "created a Web site for a bogus IRB and advertised the bogus IRB's services in newspapers and online. A real medical research company contacted the bogus IRB to get approval to join ongoing human trials involving invasive surgery -- even though GAO's investigators had no medical expertise whatsoever. Since the transaction involved privately funded human subjects research and did not involve any FDA-regulated drugs or devices, GAO's bogus IRB could have authorized this testing to begin without needing to register with any federal agency."

The full article can be found at: <http://www.gsnmagazine.com/cms/features/news-analysis/1747.html>

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TOTAL SYNTHESIS OF (-)- AND (+)-DECARBAMOYLOXYSAXITOXIN AND (+)-SAXITOXIN

News of Science

April 5, 2009

"Enantioselective total syntheses of (-)- and (+)-decarbamoxyloxysaxitoxin (doSTX) and (+)-saxitoxin (STX) were achieved," scientists writing in the Chemistry - an Asian Journal report.

"The characteristic spiro-fused cyclic guanidine structure of STX was constructed by oxidation at the C4 position with IBX via an alpha-iminium carbonyl intermediate and acid-promoted cyclization of guanidine at the C5 position. A second-generation methodology was developed for the synthesis of STX, featuring discriminative reduction of the nitro group and N-O bond in nitroisoxazolidine."

"This approach provides efficient access to the key diamine intermediate for STXs."

The full article can be found at: (O. Iwamoto, et. al., "Total Synthesis of (-)- and (+)-Decarbamoxyloxysaxitoxin and (+)-Saxitoxin". Chemistry - an Asian Journal, 2009;4(2):277-285). Link not available

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BUTYRYLCHOLINESTERASE: BIOMARKER FOR EXPOSURE TO ORGANOPHOSPHORUS INSECTICIDES

Biotech Law Weekly

April 3, 2009

'Butyrylcholinesterase: biomarker for exposure to organophosphorus insecticides.' According to a study from Goudi, Greece, "Butyrylcholinesterase (BuChE) is routinely measured to assess exposure to or effects of organophosphorus insecticides (OP). As a biomarker, it can be used to clarify the relation between exposure to OP and health impairment."

"The interpretation of BuChE inhibition data, particularly of small changes in enzymatic activity, sometimes presents significant complexities."

"Despite the complexities of their interpretation, BuChE measurements remain a mainstay for the fast initial screening of exposure to OP; thus, they are a useful tool in the protection of humans, domestic animals and wildlife from overexposure to these toxic agents."

The full article can be found at: (M. Stefanidou, et. al., "Butyrylcholinesterase: biomarker for exposure to organophosphorus insecticides". Internal Medicine Journal, 2009;39(1):57-60). Link not available.
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PREDICTION OF GAS CHROMATOGRAPHIC RETENTION INDICES OF ORGANOPHOSPHORUS COMPOUNDS BY HOLOGRAPHIC QSRR [QUANTITATIVE STRUCTURE-RETENTION RELATIONSHIP]

China Weekly News
March 31, 2009

"A new molecular structure representation, molecular hologram, is employed to investigate the quantitative relationship between gas chromatographic retention indices and molecular structures for 41 methyl-esterified organophosphorus compounds (OPs). The quantitative structure-retention relationship (QSRR) model has been constructed for GC-RI of the selected OPs through partial least squares regression, which shows high statistical quality and predictive value with non-cross validation correlation coefficient $r(2)$ of 0.994, and cross validation correlation coefficient $q(LOO)(2)$ values of 0.984."

"In order to verify the robustness and prediction capacity of the model, 30 OPs were randomly selected from the database as the training set, while the rest were used as the testing set. The result of PLS regressive analysis of the training set yields $r(2)$ of 0.995 and $q(LOO)(2)$ of 0.982, suggesting the excellent ability to predict the GC-RIs of OPs in the testing set."

"Furthermore, the retention behavior of the compounds in GC stationary phase is discussed, and the effects of different groups on the OP side-chain in the interaction between OPs and the stationary phase are explored using HQSAR color code, which provides useful guideline for the retention rules of OPs and related compounds."

The full article can be found at: (H.Y. Wang, et. al., "Prediction of gas chromatographic retention indices of organophosphorus compounds by holographic QSRR". Chinese Science Bulletin, 2009;54(4):635-641). Link not available.
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ANTHRAX PROTECTIVE ANTIGEN DELIVERED BY SALMONELLA ENTERICA SEROVAR TYPHI TY21A PROTECTS MICE FROM A LETHAL ANTHRAX SPORE CHALLENGE

TB & Outbreaks Week
March 31, 2009

"This vaccine requires six injectable doses over 18 months to stimulate protective immunity, requires a cold chain for storage, and in many cases has been associated with adverse effects. In this study, we modified the B. anthracis protective antigen (PA) gene for optimal expression and stability, linked it to an inducible promoter for maximal expression in the host, and fused it to the secretion signal of the Escherichia coli alpha-hemolysin protein (HlyA) on a low-copy-number plasmid. This plasmid was introduced into the licensed typhoid vaccine strain, Salmonella enterica serovar Typhi strain Ty21a, and was found to be genetically stable. Immunization of mice with three vaccine doses elicited a strong PA-specific serum immunoglobulin G response with a geometric mean titer of 30,000 (range, 5,800 to 157,000) and lethal-toxin-neutralizing titers greater than 16,000. Vaccinated mice demonstrated 100%

protection against a lethal intranasal challenge with aerosolized spores of *B. anthracis* 7702."

"The ultimate goal is a temperature-stable, safe, oral human vaccine against anthrax infection that can be self-administered in a few doses over a short period of time."

The full article can be found at: (M. Osorio, et. al., "Anthrax protective antigen delivered by *Salmonella enterica* serovar Typhi Ty21a protects mice from a lethal anthrax spore challenge". *Infection and Immunity*, 2009;77(4):1475-82). Link not available.

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CHARACTERIZATION OF VIBRIO CHOLERAЕ OUTER MEMBRANE VESICLES AS A CANDIDATE VACCINE FOR CHOLERA

Vaccine Weekly

April 1, 2009

"Outer membrane vesicles (OMVs) offer a new approach for an effective cholera vaccine. We recently demonstrated that immunization of female mice with OMVs induces a long-lasting immune response and results in protection of their neonatal offspring from *Vibrio cholerae* intestinal colonization," researchers in the United States report (see also Cholera).

"This study investigates the induced protective immunity observed after immunization with OMVs in more detail. Analysis of the stomach contents and sera of the neonates revealed significant amounts of anti-OMV immunoglobulins (Igs). Swapping of litters born to immunized and nonvaccinated control mice allowed us to distinguish between prenatal and neonatal uptakes of Igs. Transfer of Igs to neonates via milk was sufficient for complete protection of the neonates from colonization with *V. cholerae*, while prenatal transfer alone reduced colonization only. Detection of IgA and IgG1 in the fecal pellets of intranasally immunized adult mice indicates an induced immune response at the mucosal surface in the gastrointestinal tract, which is the site of colonization by *V. cholerae*. When a protocol with three intranasal immunizations 14 days apart was used, the OMVs proved to be efficacious at doses as low as 0.025 μ g per immunization. This is almost equivalent to OMV concentrations found naturally in the supernatants of LB-grown cultures of *V. cholerae*. Heterologous expression of the periplasmic alkaline phosphatase (PhoA) of *Escherichia coli* resulted in the incorporation of PhoA into OMVs derived from *V. cholerae*. Intranasal immunization with OMVs loaded with PhoA induced a specific immune response against this heterologous antigen in mice."

The detection of an immune response against this heterologously expressed protein is a promising step toward the potential use of OMVs as antigen delivery vehicles in vaccine design."

The full article can be found at: (S. Schild, et. al., "Characterization of *Vibrio cholerae* Outer Membrane Vesicles as a Candidate Vaccine for Cholera". *Infection and Immunity*, 2009;77(1):472-484). Link not available.

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CHIP MIMICS METABOLISM

By Madelaine Chapman

Chemical Technology (UK Royal Society of Chemistry)

April 1, 2009

"Drug metabolism studies can be conducted on smaller samples than before thanks to an on-chip electrochemical cell designed by European scientists."

"Mathieu Odijk, at the University of Twente, Enschede, the Netherlands, and colleagues made a glass chip containing the usual three electrodes found in an electrochemical cell - the working, reference and counter electrodes - plus an extra sensing electrode to detect generated species. They connected the chip to a liquid chromatography-mass spectrometry (LC-MS) system. When they injected a solution of

amodiaquine, an antimalarial drug, through the chip, they showed that the cell oxidised the drug, forming all its major metabolites, which were detected by LC-MS.”

The full article can be found at:

http://www.rsc.org/Publishing/ChemTech/Volume/2009/05/chip_metabolism.asp

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