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Chem-Bio News – S&T Edition

1. DRAMATIC DIFFERENCES IN ORGANOPHOSPHORUS HYDROLASE ACTIVITY BETWEEN HUMAN AND CHIMERIC RECOMBINANT MAMMALIAN PARAOXONASE-1 ENZYMES:

"We have identified the first variant of HuPON1, H115W, that displays significantly enhanced catalytic activity against an authentic V-type nerve agent."

2. PHARMATHENE PRESENTS PHASE I CLINICAL TRIAL RESULTS AND NEW THERAPEUTIC ANIMAL MODEL DATA FOR PROTEXIA®:

"PharmAthene, Inc. announced Phase I clinical trial results for Protexia=AE, a pegylated recombinant version of human butyrylcholinesterase (rBChE), which has been shown to be effective in animal models in preventing toxicity from exposure to chemical nerve agents."

3. AN EVALUATION OF SUSPICIOUS POWDER SCREENING TOOLS FOR FIRST RESPONDERS:

"In this study, three commercially available generic screening technologies were evaluated for the effectiveness to accurately differentiate between a hoax powder and a true biological threat."

4. BIOMONITORING OF ORGANOPHOSPHORUS AGENT EXPOSURE BY REACTIVATION OF CHOLINESTERASE ENZYME BASED ON CARBON NANOTUBE-ENHANCED FLOW-INJECTION AMPEROMETRIC DETECTION:

"Since it excludes inter- or intraindividual variation in the normal levels of ChE, this new CNT-based electrochemical sensor thus provides a sensitive and quantitative tool for point-of-care assessment and noninvasive biomonitoring of the exposure to OP pesticides and chemical nerve agents."

5. COMPUTATIONAL DESIGN AND MULTISCALE MODELING OF A NANOACTUATOR USING DNA ACTUATION:

"Based on the analysis of the simulation results, a servo nanoactuator using ionic current feedback is simulated and analyzed for application as a drug delivery carrier."

6. EXPANSION, REEXPANSION, AND RECALL-LIKE EXPANSION OF V GAMMA 2V DELTA 2 T CELLS IN SMALLPOX VACCINATION AND MONKEYPOX VIRUS INFECTION:

"Our studies provide the first in vivo evidence that viruses, despite their inability to produce exogenous phosphoantigen, can induce expansion, reexpansion, and

recall-like expansion of V gamma 2V delta 2 T cells and stimulate their antimicrobial cytokine response."

7. EFFICACY AND SAFETY OF A MODIFIED KILLED-WHOLE-CELL ORAL CHOLERA VACCINE IN INDIA: AN INTERIM ANALYSIS OF A CLUSTER-RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL:

"This modified killed-whole-cell oral vaccine, compliant with WHO standards, is safe, provides protection against clinically significant cholera in an endemic setting, and can be used in children aged 1.0-4.9 years, who are at highest risk of developing cholera in endemic settings."

CB Daily Report

Chem-Bio News

DRAMATIC DIFFERENCES IN ORGANOPHOSPHORUS HYDROLASE ACTIVITY BETWEEN HUMAN AND CHIMERIC RECOMBINANT MAMMALIAN PARAOXONASE-1 ENZYMES

Chemical & Chemistry
December 18, 2009

"Human serum paraoxonase-1 (HuPON1) has the capacity to hydrolyze aryl esters, lactones, oxidized phospholipids, and organophosphorus (OP) compounds. HuPON1 and bacterially expressed chimeric recombinant PON1s (G2E6 and G3C9) differ by multiple amino acids, none of which are in the putative enzyme active site."

"To address the importance of these amino acid differences, the abilities of HuPON1, G2E6, G3C9, and several variants to hydrolyze phenyl acetate, paraoxon, and V-type OP nerve agents were examined. HuPON1 and G2E6 have a 10-fold greater catalytic efficiency toward phenyl acetate than G3C9. In contrast, bacterial PON1s are better able to promote hydrolysis of paraoxon, whereas HuPON1 is considerably better at catalyzing the hydrolysis of nerve agents VX and VR. These studies demonstrate that mutations distant from the active site of PON1 have large and unpredictable effects on the substrate specificities and possibly the hydrolytic mechanisms of HuPON1, G2E6, and G3C9. The replacement of residue H115 in the putative active site with tryptophan (H115W) has highly disparate effects on HuPON1 and G2E6. In HuPON1, variant H115W loses the ability to hydrolyze VR but has improved activity toward paraoxon and VX. The H115W variant of G2E6 has paraoxonase activity similar to that of wild-type G2E6, modest activity with phenyl acetate and VR, and enhanced VX hydrolysis. VR inhibits H115W HuPON1 competitively when paraoxon is the substrate and noncompetitively when VX is the Substrate."

"We have identified the first variant of HuPON1, H115W, that displays significantly enhanced catalytic activity against an authentic V-type nerve agent."

The full article can be found at: (T.C. Otto, et. al., "Dramatic Differences in Organophosphorus Hydrolase Activity between Human and Chimeric Recombinant Mammalian Paraoxonase-1 Enzymes". *Biochemistry*, 2009; 48(43): 10416-10422). Link not available.

PHARMATHENE PRESENTS PHASE I CLINICAL TRIAL RESULTS AND NEW THERAPEUTIC ANIMAL MODEL DATA FOR PROTEXIA®

Drug Week

December 25, 2009

"PharmAthene, Inc. announced Phase I clinical trial results for Protexia=AE, a pegylated recombinant version of human butyrylcholinesterase (rBChE), which has been shown to be effective in animal models in preventing toxicity from exposure to chemical nerve agents. The results were presented in an oral presentation on Friday, December 4, 2009, at the Health and Human Services Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Stakeholders Workshop 2009 / BARDA Industry Day, in Washington, D.C."

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"The Phase I clinical study was a randomized, placebo-controlled, third-party double-blind, dose-escalating study conducted to assess the safety and tolerability of Protexia=AE administered intramuscularly at one or two time points in healthy human volunteers. Under the study protocol, either Protexia=AE or a saline placebo was administered in escalating doses to six groups of volunteers. A total of 33 subjects participated in the study; 22 of these subjects were treated with Protexia and 11 were treated with saline placebo. Five of the six dose groups (15 volunteers) received a single intramuscular (IM) dose of Protexia ranging from 50 to 750 mg. Subjects in the 250mg dose cohort (7 volunteers) received a second dose of Protexia=AE 72 days following the first dose.

The Phase I data showed that Protexia=AE was safe and well-tolerated. No serious adverse events were reported. The most common adverse events reported in the subjects receiving Protexia were injection site reactions, occurring in 19 of 22 volunteers.

As Protexia=AE was well-tolerated in the study, with no significant safety issues and no evidence of immunogenicity, these data suggest that Protexia=AE may be a promising new approach to the prophylaxis and treatment of nerve agent toxicity.

In addition, preclinical studies of Protexia=AE in animals have suggested that it has the potential to provide significant protection against chemical nerve agent poisoning when administered prophylactically (prior to exposure to nerve agent) and also may increase survival when administered therapeutically (following nerve agent exposure).

PharmAthene has been collaborating with The Defense Science and Technology Laboratory (Dstl) on preclinical studies to investigate the therapeutic efficacy of Protexia=AE. New data from these studies were also presented at the PHEMCE conference. In a collaborative poster with Dstl entitled, "Post-Poisoning Treatment with Recombinant Butyrylcholinesterase Reduces VX Blood Concentration and Prevents VX-Induced Mortality," investigators conducted research to determine the utility of rBChE as a post-nerve agent poisoning medical countermeasure in two guinea pig models.

Each of the models provided different assessments of exposure to organophosphorus nerve agent (VX) on the skin. In the first model, male guinea pigs were implanted with dermal and blood microdialysis probes to monitor nerve agent concentration in these tissues following exposure to VX. In a separate model, telemetry transponders were surgically implanted in animals to monitor the effects of exposure to VX on physiological parameters. VX was applied to the dorsal skin of the guinea pigs and rBChE or vehicle control was administered 30 or 120 minutes later.

Animals treated with rBChE 30 minutes post VX exposure had lower blood concentrations of VX than vehicle treated control animals. Additionally, treatment with rBChE 2 hours post VX exposure mitigated the physiological changes observed in vehicle treated animals, in addition to preventing lethality.

"The majority of our research to date for Protexia=AE (rBChE) has focused on studying its efficacy as a pre-exposure prophylactic. These results provide further encouraging evidence for the utility of post-poisoning treatment with rBChE. We plan to undertake further work to build upon these findings and define the window of therapeutic efficacy provided by treatment with rBChE," continued Mr. Wright."

Link not available.

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AN EVALUATION OF SUSPICIOUS POWDER SCREENING TOOLS FOR FIRST RESPONDERS

Energy & Ecology

December 25, 2009

"Field screening tools are required which would allow first responders to quickly ascertain if a suspicious powder poses a potential threat necessitating additional testing for biological pathogens such as *Bacillus anthracis*. In this study, three commercially available generic screening technologies were evaluated for the effectiveness to accurately differentiate between a hoax powder and a true biological threat."

"The BioCheck® Kit was able to detect the following biological agents 1 x 10⁽⁸⁾ CFU of *B. anthracis* Sterne (washed 4 times), 1 x 10⁽⁷⁾ CFU of *B. anthracis* Delta Sterne (washed 2 times), 1 x 10⁽⁷⁾ CFU of *Yersinia pestis* All 122, and 100 µg of ricin. The PrimeAlert(TM) kit was able to detect 2 x 10⁽¹⁰⁾ CFU of *B. anthracis* Delta Sterne 4x, 1 x 10⁹ CFU of *B. anthracis* Delta Sterne 2 x, and 1 x 10⁽⁸⁾ CFU of *Y. pestis* A1122. The Prime Alert(TM) kit was not able to detect ricin. The Profile®-1 kit was able to detect 1 x 10⁽⁴⁾ CFU of *B. anthracis* Delta Sterne 4x and *B. anthracis* Delta Sterne 2x, and 1 x 10⁽⁶⁾ CFU of *Y. pestis* A1122. The Profile®-1 kit was not able to detect ricin. All of the kits showed positive results for powders containing components specifically targeted by the particular technology being used."

The full article can be found at: (C. Poor, et. al., "An evaluation of suspicious powder

screening tools for first responders". *Journal of Hazardous Materials*, 2009; 172(2-3):559-565). Link not available.

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BIOMONITORING OF ORGANOPHOSPHORUS AGENT EXPOSURE BY REACTIVATION OF CHOLINESTERASE ENZYME BASED ON CARBON NANOTUBE-ENHANCED FLOW-INJECTION AMPEROMETRIC DETECTION

Drug Week

December 18, 2009

"A portable, rapid, and sensitive assessment of subclinical organophosphorus (OP) agent exposure based on reactivation of cholinesterase (ChE) from OP-inhibited ChE using rat saliva (in vitro) was developed using an electrochemical sensor coupled with a microflow-injection system. The sensor was based on a carbon nanotube (CNT)-modified screen printed carbon electrode (SPE), which was integrated into a flow cell."

"Because of the extent of interindividual ChE activity variability, ChE biomonitoring often requires an initial baseline determination (noninhibited) of enzyme activity which is then directly compared with activity after OP exposure. This manuscript describes an alternative strategy where reactivation of the phosphorylated enzyme was exploited to enable measurement of both inhibited and baseline ChE activity (after reactivation by an oxime, i. e., pralidoxime iodide) in the same sample. The use of CNT makes the electrochemical detection of the products from enzymatic reactions more feasible with extremely high sensitivity (5% ChE inhibition) and selectivity. Paraoxon was selected as a model OP compound for in vitro inhibition studies. Some experimental parameters, e.g., inhibition and reactivation time, have been optimized such that 92-95% of ChE reactivation can be achieved over a broad range of ChE inhibition (5-94%) with paraoxon. The extent of enzyme inhibition using this electrochemical sensor correlates well with conventional enzyme activity measurements. On the basis of the double determinations of enzyme activity, this flow-injection device has been successfully used to detect paraoxon inhibition efficiency in saliva samples (95% of ChE activity is due to butyrylcholinesterase), which demonstrated its promise as a sensitive monitor of OP exposure in biological fluids."

"Since it excludes inter- or intraindividual variation in the normal levels of ChE, this new CNT-based electrochemical sensor thus provides a sensitive and quantitative tool for point-of-care assessment and noninvasive biomonitoring of the exposure to OP pesticides and chemical nerve agents."

The full article can be found at: (D. Du, et. al., "Biomonitoring of Organophosphorus Agent Exposure by Reactivation of Cholinesterase Enzyme Based on Carbon Nanotube-Enhanced Flow-Injection Amperometric Detection". *Analytical Chemistry*, 2009; 81(22):9314-9320). Link not available.

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COMPUTATIONAL DESIGN AND MULTISCALE MODELING OF A NANOACTUATOR USING DNA ACTUATION

Journal of Technology & Science

December 13, 2009

"Developments in the field of nano-biodesigns coupling nanostructures and biological components are of great interest in medical nanorobotics. As the fundamentals of bio/non-bio interaction processes are still poorly understood in the design of these devices, design tools and multiscale dynamics modeling approaches are necessary at the fabrication pre-project stage."

"This paper proposes a new concept of optimized carbon nanotube based servomotor design for drug delivery and biomolecular transport applications. The design of an encapsulated DNA-multi-walled carbon nanotube actuator is prototyped using multiscale modeling. The system is parametrized by using a quantum level approach and characterized by using a molecular dynamics simulation."

"Based on the analysis of the simulation results, a servo nanoactuator using ionic current feedback is simulated and analyzed for application as a drug delivery carrier."

The full article can be found at: (M. Hamdi, et. al., "Computational design and multiscale modeling of a nanoactuator using DNA actuation". Nanotechnology, 2009;20(48):85501). Link not available.

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EXPANSION, REEXPANSION, AND RECALL-LIKE EXPANSION OF V GAMMA 2V DELTA 2 T CELLS IN SMALLPOX VACCINATION AND MONKEYPOX VIRUS INFECTION

Drug Week

December 18, 2009

"Little is known about the in vivo kinetics of T-cell responses in smallpox/monkeypox. We showed that macaque V gamma 2V delta 2 T cells underwent 3-week-long expansion after smallpox vaccine immunization and displayed simple reexpansion in association with sterile anti-monkeypox virus (anti-MPV) immunity after MPV challenge."

"Virus-activated V gamma 2V delta 2 T cells exhibited gamma interferon-producing effector function after phosphoantigen stimulation. Surprisingly, like alpha beta T cells, suboptimally primed V gamma 2V delta 2 T cells in vaccinia virus/cidofovir-covaccinated macaques mounted major recall-like expansion after MPV challenge. Finally, V gamma 2V delta 2 T cells localized in inflamed lung tissues for potential regulation."

"Our studies provide the first in vivo evidence that viruses, despite their inability to produce exogenous phosphoantigen, can induce expansion, reexpansion, and recall-like expansion of V gamma 2V delta 2 T cells and stimulate their antimicrobial cytokine response."

The full article can be found at: (L.Y. Shao, et. al., "Expansion, Reexpansion, and Recall-Like Expansion of V gamma 2V delta 2 T Cells in Smallpox Vaccination and Monkeypox Virus Infection". Journal of Virology, 2009;83(22):11959-11965). Link not available.

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EFFICACY AND SAFETY OF A MODIFIED KILLED-WHOLE-CELL ORAL CHOLERA VACCINE IN INDIA: AN INTERIM ANALYSIS OF A CLUSTER-RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

Biotech Week

December 23, 2009

"Oral cholera vaccines consisting of killed whole cells have been available for many years, but they have not been used extensively in populations with endemic disease. An inexpensive, locally produced oral killed-whole-cell vaccine has been used in high-risk areas in Vietnam."

"To expand the use of this vaccine, it was modified to comply with WHO standards. We assessed the efficacy and safety of this modified vaccine in a population with endemic cholera. In this double-blind trial, 107 774 non-pregnant residents of Kolkata, India, aged 1 year or older, were cluster-randomised by dwelling to receive two doses of either modified killed-whole-cell cholera vaccine (n=52212; 1966 clusters) or heat-killed Escherichia coli K12 placebo (n=55 562; 1967 clusters), both delivered orally. Randomisation was done by computer-generated sequence in blocks of four. The primary endpoint was prevention of episodes of culture-confirmed Vibrio cholerae 01 diarrhoea severe enough for the patient to seek treatment in a health-care facility. We undertook an interim, per-protocol analysis at 2 years of follow-up that included individuals who received two completely ingested doses of vaccine or placebo. We assessed first episodes of cholera that occurred between 14 days and 730 days after receipt of the second dose. This study is registered with ClinicalTrials.gov, number NCT00289224. 31932 participants assigned to vaccine (1721 clusters) and 34 968 assigned to placebo (1757 clusters) received two doses of study treatment. There were 20 episodes of cholera in the vaccine group and 68 episodes in the placebo group (protective efficacy 67%; one-tailed 99% CI, lower bound 35%, p<0.0001). The vaccine protected individuals in age-groups 1.0-4.9 years, 5.0-14.9 years, and 15 years and older, and protective efficacy did not differ significantly between age-groups (p=0.28). We recorded no vaccine-related serious adverse events."

"This modified killed-whole-cell oral vaccine, compliant with WHO standards, is safe, provides protection against clinically significant cholera in an endemic setting, and can be used in children aged 1.0-4.9 years, who are at highest risk of developing cholera in endemic settings."

The full article can be found at: (D. Sur, et. al., "Efficacy and safety of a modified killed-whole-cell oral cholera vaccine in India: an interim analysis of a cluster-randomised, double-blind, placebo-controlled trial". Lancet, 2009;374(9702):1694-1702). Link not available.

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