United States Patent Granted to Biotranex for BSEPcyte™ Assay

Monmouth Junction, NJ, 11 July 2017 – Biotranex, LLC is pleased and excited to announce the allowance of its patent application entitled “Method for Measuring Bile Salt Export Transport and/or Formation Activity” Application Number 14/781520 filed on September 30, 2015 by the United States Patent and Trademark Organization (USPTO). The patent claims are directed to Biotranex’s hepatocyte suspension assay named BSEPcyte™. Dr. Kan He of Biotranex is the inventor of this novel and unique assay which allows for the measurement of inhibition of the bile salt export protein (BSEP or ABCB11) by test agents using suspensions of primary hepatocytes. Dr. He points out that BSEPcyte™ has significant advantages over other BSEP assays including:
- Physiologically relevant hepatocyte suspension platform
- Accurate, robust, reproducible, and customizable
- Cross species comparison
- In situ Metabolism capability
- Specific LC-MS/MS quantitation of exported bile salts
- and Cost

About Biotranex, LLC

Biotranex is an innovative service company that commercializes novel and proprietary assays for research in hepatic transport, cholestasis, drug-induced liver injury, drug interactions, and drug metabolism. Biotranex offers an extensive array of drug metabolism, pharmacokinetics and analytical services. For additional information, please contact Dr. Kan He, President, Biotranex, LLC, 9 Deer Park Drive, Suite A-1, Monmouth Junction, NJ 08852 at Khe@biotranex.com or call (732) 230-3062.

SURMOUNTING THE INSURMOUTABLE IS A BIG SUCCESS AT EXPERIMENTAL BIOLOGY 2017

Monmouth Junction, NJ, April 26, 2017. In 2016 the American Society of Pharmacology and Experimental Therapeutics (ASPET) approved a “Big Idea” initiative created and developed by Drs Kan He and Thomas F. Woolf of Biotranex and group of leading academic and industrial
though leaders, for purposes of a special session to be held as part of the annual Experimental Biology (EB) meeting to address an educational need that ASPET deemed would ultimately serve the broader community of ASPET members as well as the discipline of pharmacology. The main purpose of this special session is to provide a forum for pharmacological experts to present "real world" stories recounting when, in their own experience, insurmountable problems arose that became what appeared to be an "insurmountable obstacle" in the development of a drug they and their team were developing. The presenter would then explain how critical thinking and problem-solving skills were used to overcome the problem and allow the drug development process to continue. Each session comprises three to four presentations with a follow up Q&A. The special session under the title "Surmounting the Insurmountable: Obstacles in Drug Discovery and Development – Real World Case Studies" held its inaugural session in April in Chicago as part of the EB2017 meeting and was an immediate success.

Dr Kan He of Biotranex and Emeritus Professor Paul Hollenberg of the University of Michigan co-chaired the inaugural session. The presenters and their topics included a wide variety of challenging cases as told by experienced and notable scientists. As part of this session, Dr Kan He gave a presentation titled “Apixaban: How Volume of Distribution Became Critical in Optimizing Efficacy and Minimizing Toxicity” where he described the surprising role volume of distribution was in the discovery and development of the anti-coagulant Apixiban.

Biotranex and Pfizer Published Positive Results for Use of the MDR3 cyte™ assay in Predicting Drug-Induced Liver Injury in a Study Using 125 Pharmaceutical Drugs


The role of bile salt export protein (BSEP) inhibition in drug-induced liver injury (DILI) has been
investigated widely, while inhibition of the canalicular multidrug resistant protein 3 (MDR3) has received less attention. This transporter plays a pivotal role in secretion of phospholipids into bile and functions coordinately with BSEP to mediate the formation of bile acid-containing biliary micelles. Therefore, inhibition of MDR3 in human hepatocytes was examined across 125 drugs (70 of Most-DILI-concern and 55 of No-DILI-concern). In conclusion, avoiding physical property descriptors that highlight dual BSEP and MDR3 inhibition or testing drug candidates for inhibition of multiple efflux transporters (e.g., BSEP, MDR3, and MRPs) may be an effective strategy for prioritizing drug candidates with less likelihood of causing clinical DILI. This research was a collaboration between scientists at Biotranex and Pfizer.

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Biotranex Announces the Publication of a Research Paper on Predicting Drug-Induced Liver Toxicity Employing the BSEPcyteTM Assay


Drug-induced liver injury (DILI) is a severe adverse drug response which cannot always be reliably predicted in preclinical or clinical studies. Lack of observation of DILI during preclinical and clinical drug development has led to DILI being a leading cause of drug withdrawal from the market. In vitro inhibition of the bile salt export pump (BSEP) has become a major risk factor for in vivo DILI predictions, yet discrepancies exist in which methods to use and the extent to which BSEP inhibition predicts clinical DILI. The presented work in this important study focused on the optimization of DILI predictions by the hepatocyte suspension BSEPcyteTM assay. This research was a collaboration between scientists at Biotranex and Taketa.
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Biotranex Announces the Presentation of BSEPcyte™ and MDR3cyte™ Assays for Screening Hepatotoxic Drugs and Assessing Species Differences


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Biotranex Announces the Presentation of Novel BSEP and MDR3 Assays Using Primary Hepatocytes for Screening DILI
Monmouth Junction, NJ, 16 May 2016 - Biotranex, LLC is pleased to announce the presentation of a talk at the Experimental Biology (EB) annual meeting in San Diego by Dr Kan He entitled “Novel BSEP and MDR3 Assays Using Primary Hepatocytes for Screening DILI Drugs and Species Differences.” Hepatic multidrug resistance protein 3 (MDR3, ABCB4) and bile salt export pump protein (BSEP, ABCB11) are primarily responsible for biliary secretion of phosphatidylcholine and bile salts, respectively. Accumulated evidence indicates that inhibition of MDR3 and BSEP activities is associated with drug-induced liver injury (DILI). BSEP inhibition assay employing membrane vesicles prepared from BSEP transfected insect cells has issues of physiological relevance, while the BSEP inhibition assay using human sandwich cultured hepatocytes (SCH), has limitations due to technical complexity, reproducibility, low throughput, and high cost. Current MDR3 inhibition assays include transfected cell lines and membrane vesicles prepared from MDR3 transfected insect cells. These MDR3 assays also suffer from issues of physiological relevance. Here we presented data supporting the development and validation of BSEP cyte™ and MDR3cyte™ assays and the application of these assays to testing DILI drugs and species differences. These results showed the physiological relevance of BSEP cyte™ and MDR3 cyte™, in vitro in vivo extrapolation, accuracy, reproducibility, large dynamic range and ability to measure in situ metabolism of test DILI drugs. Cross species studies show differences in BSEP inhibition for several test DILI drugs that may explain, at least in part, species differences in DILI.

BSEPcyte™ and MDR3cyte™ are patent-pending assays that offer significant advantages over other currently available methodologies. They are both physiologically relevant hepatocyte-based systems that allow measurement of drug candidate inhibition of human BSEP and MDR3, provide for cross-species studies, and offer the ability to investigate the effect of drug metabolism on inhibition; both assays are also run without radioactive reagents.

About Biotranex, LLC

Biotranex is an innovative biotechnology discovery and service company that commercializes novel and proprietary assays for research in hepatic transport, cholestasis, drug-induced liver injury, drug interactions, and drug metabolism. Biotranex also offers an extensive array of drug
Biotranex Announces the Presentation of BSEPyte™ and MDR3pyte™: Novel BSEP and MDR3 Inhibition Assays for Screening DILI Drugs at the 2016 Annual Workshop and Conference: Novel In Vitro ADMET Technologies for Drug Development in Malden, MA

Monmouth Junction, NJ, 16 May 2016 - Biotranex, LLC is pleased to announce the presentation of a talk at the 2016 Annual Workshop and Conference: Novel In Vitro ADMET Technologies for Drug Development in Malden, MA by Dr Kan He entitled “BSEPpyte™ and MDR3pyte™ Novel BSEP and MDR3 Inhibition Assays for Screening DILI Drugs.” Hepatic multidrug resistance protein 3 (MDR3, ABCB4) and bile salt export pump protein (BSEP, ABCB11) are primarily responsible for biliary secretion of phosphatidylcholine and bile salts, respectively. Accumulated evidence indicates that inhibition of MDR3 and BSEP activities is associated with drug-induced liver injury (DILI). The presentation described the development and validation of BSEPpyte™ and MDR3pyte™ assays and the application of these assays to testing DILI drugs and species differences. Specifically, the presentation showed experimental results on the physiological relevance of BSEPpyte™ and MDR3pyte™, in vitro in vivo extrapolation, accuracy, reproducibility, large dynamic range and ability to measure in situ metabolism of test drugs. Cross species studies show differences in BSEP inhibition for several test DILI drugs that may explain, at least in part, species differences in DILI.

BSEPpyte™ and MDR3pyte™ are patent-pending assays that offer significant advantages over other currently available methodologies. They are both physiologically relevant hepatocyte-based systems that allow measurement of drug candidate inhibition of human BSEP and MDR3, provide for cross-species studies, and offer the ability to investigate the effect of drug metabolism on inhibition; both assays are also run without radioactive reagents.
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**Biotranex Announces the Publication of “Inhibition of bile salt transport by drugs associated with liver injury in primary hepatocytes from human, monkey, dog, rat, and mouse” in Chemico-Biological Interactions**

**Monmouth Junction, NJ, 16 May 2016** - Biotranex, LLC is pleased to announce the online publication of the paper entitled “Inhibition of bile salt transport by drugs associated with liver injury in primary hepatocytes from human, monkey, dog, rat, and mouse” by Drs Jie Zhang (US FDA), Kan He (Biotranex, LLC) et al. in Chemico-Biological Interactions 2016 Mar 19 pii: S0009-2797(16)30089-8. doi: 10.1016/j.cbi.2016.03.019. [Epub ahead of print]. Interference of bile salt transport is one of the underlying mechanisms for drug-induced liver injury (DILI). We developed a novel bile salt transport activity assay involving in situ biosynthesis of bile salts from their precursors in primary human, monkey, dog, rat, and mouse hepatocytes in suspension as well as LC-MS/MS determination of extracellular bile salts transported out of hepatocytes. The assay was used to test 86 drugs for their potential to inhibit bile salt transport activity in human hepatocytes, which included 35 drugs associated with severe DILI (sDILI) and 51 with non-severe DILI (non-sDILI). Approximately 60% of the sDILI drugs showed potent inhibition (with IC50 values


Yucha RW, He K, Shi Q, Cai L, Nakashita Y, Xia CQ, Liao M. **In Vitro Drug-Induced Liver**
Injury Prediction: Criteria Optimization of Efflux Transporter IC50 and Physicochemical Properties


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Patents
