Biotranex President Organizes Session on Overcoming Drug Development Obstacles at 2018 Experimental Biology Meeting

Monmouth Junction, NJ, April 26, 2018 Biotranex President Dr. Kan He organized and co-chaired the session “Surmounting the Insurmountable: Obstacles in Drug Discovery and Development - Real World Case Studies” at the 2018 Experimental Biology (EB) Meeting, held in San Diego, CA, from April 21-25. EB is the annual meeting of five societies comprised of more than 14,000 scientists and 25 guest societies, and open to everyone with interest in the latest research impacting life sciences. Dr. He’s session examined how scientists can overcome obstacles in drug development through problem-solving and critical thinking skills. Dr. He co-chaired the session with Dr. Paul F. Hollenburg, Professor Emeritus of the University of Michigan.

This year’s session featured four different case-studies, presented by four speakers from various pharmaceutical companies. (The session is covered on page 91 of the June 2018 issue of The Pharmacologist.) Speakers shared their stories of unexpected roadblocks they faced during the drug development process and how they overcame these.

The session is sponsored by the ASPET BIG IDEAS Initiative, started in 2014 to encourage members to create projects directly benefitting the general ASPET membership. Dr. He says in the EB TV video released shortly after the 2018 session, “The session really provides the opportunity for scientists to learn from each other and also allows the scientists who have developed those skills and have the experience, to share to [sic] other scientists.” Scientists who attended this session have garnered valuable lessons from their peers on how to use critical thinking and problem-solving in their own drug development journeys.

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.
Biotranex Presents Poster and Sponsors Booth at International Society for the Study of Xenobiotics’ Annual Meeting

Monmouth Junction, NJ, July 20, 2018. Biotranex showcased its discoveries at the International Society for the Study of Xenobiotics’ (ISSX) annual North American meeting, held in Montréal, Québec, from July 15-19, 2018. ISSX has an international base of members from more than 45 countries. Biotranex presented a poster titled “Apparent Noncompetitive Inhibition of BSEP in Primary Human Hepatocytes Associated with Severe Drug-Induced Liver Injury”, and received wide responses. Biotranex also sponsored a booth in order to exhibit its drug discovery and development services. These services include Biotranex’s proprietary assay formats, BSEPcyte®, MDR3cyte®, and BILIRUBINcyte™.

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Biotranex LLC Granted Patent for Bile Salt Export Protein BSEP cyte™ Assay


MONMOUTH JUNCTION, N.J., Oct. 4, 2017 /PRNewswire/ -- Biotranex LLC, an innovative contract research laboratory and a leader in developing and offering drug transporter assays, today announced that the United States Patent and Trademark Office (USPTO) has granted the Company United States patent number 9,772,325, covering its novel bile salt export protein
(BSEP) inhibition assay that is marketed as BSEP cyte™.

Drugs that inhibit BSEP are implicated in cholestasis and drug-induced liver injuries (DILI), which has led to the costly withdrawal of several marketed drugs. A unique aspect of the BSEP cyte™ assay platform is that it utilizes hepatocytes in suspension to measure BSEP inhibition. This platform is accurate, reproducible, and flexible as well as cost competitive.

"BSEP cyte™ offers significant advantages over other currently available methodologies"

A physiologically relevant hepatocyte-based system, BSEP cyte™ allows for the measurement of drug candidate inhibition of human BSEP, provides for cross-species studies, and offers the ability to investigate the effect of drug metabolism on inhibition. Notably, this assay is also run without radioactive reagents. The BSEP cyte™ assay is a better, safer, faster option to other assays currently on the market.

Another distinguishing advantage is that the BSEP cyte™ assay can be used as part of an early screening strategy in drug discovery, or later in drug development to provide more detailed investigations, including metabolism and cross-species studies.

This novel patent is critical in the development phase of new drugs because when bile salt export protein (BSEP) liver transporter is inhibited, drug-induced liver injury (DILI) can result. Drug-induced liver injury encompasses a spectrum of toxicities ranging from mild biochemical abnormalities to acute liver failure, and in some cases, the need for a liver transplant. DILI is responsible not only for the withdrawal of several marketed drugs but also for the necessity of FDA black box warning labels.

"The role that inhibition of liver transporters, including BSEP, plays in cholestasis and drug-induced liver injury is only recently being appreciated by drug developers in the pharmaceutical and biotech industries," states Dr. Kan He. "Preclinical animal models are poor
predictors of DILI in human subjects. A major cause of DILI and cholestasis is the inhibition of human bile salt export protein. Therefore, it is critical to accurately determine the inhibition potential of this human hepatic transport protein for new drug candidates.

The BSEPcyte™ assay employs a platform using suspensions of human or animal hepatocytes in a 96-well plate format with liquid chromatography-mass spectrometry quantification. The assay is reproducible, sensitive, flexible, robust, and possesses a wide dynamic concentration range. The assay shows excellent correlation with drugs found to inhibit BSEP and that may cause human cholestasis and DILI.

Dr. He further states, "We are pleased to introduce this validated BSEPcyte™ assay methodology to provide significant physiological and technical advantages over other assays, while being cost competitive."

**About Biotranex LLC**

Dr. Kan He, President of Biotranex LLC and inventor of the BSEPcyte™ assay, has specialized in research focused on drug metabolism, transporters, and liver toxicity in support of drug discovery and development during an extensive career. His work has evolved at Warner-Lambert Co., Dupont Pharmaceuticals, and Bristol Myers Squibb (BMS), where he played a key role in the discovery of the oral anticoagulant apixaban. Dr. He co-founded two biotech drug discovery companies prior to establishing Biotranex LLC in the United States. Dr. He's work has been published extensively in the fields of drug metabolism and transporters.

Biotranex LLC is an innovative contract 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 metabolism, transport, pharmacokinetic, and analytic services to the biotech and pharmaceutical industries. The extensive collective experience in the successful discovery and development of marketed drugs allows Biotranex to apply innovative solutions to the ADME/PK needs of other companies. The company's offices are located near Princeton, New Jersey, in Monmouth Junction. [http://www.biotranex.com](http://www.biotranex.com).

**Contacts:**

Kan He, Ph.D. - President
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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 BSEP cyte™. 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 BSEP cyte™ 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

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--- 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.

https://www.aspet.org/About_ASPET/ASPET_BIG_IDEAS_Initiative/
https://www.aspet.org/Annual_Meeting_EB_2017/Program/Tuesday_April_25_2017/

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**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**


http://pubs.acs.org/doi/abs/10.1021/acs.chemrestox.7b00048
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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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.

BSEP cyte™ and MDR3 cyte™ 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 Presentation of BSEPcyte™ and MDR3cyte™: 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 “BSEPcyte™ and MDR3cyte™ 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 BSEPcyte™ and MDR3cyte™ 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 BSEPcyte™ and MDR3cyte™, 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.
BSEP cyte™ and MDR3 cyte™ 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


http://link.springer.com/article/10.1007%2Fs40256-015-0145-0


http://pubs.acs.org/doi/10.1021/acs.chemrestox.5b00201


**Patents**
