Recently, the University of Kansas startup company CyDex Pharmaceuticals Inc. announced that Nexterone received new drug application approval from the U.S. Food and Drug Administration. The Nexterone formulation is based on the patent-protected CyDex Captisol technology platform. Nexterone is the first CyDex proprietary product to achieve the milestone of new drug application approval. CyDex was created in 1993 to market drug formulation technologies developed at KU. Nexterone will be marketed exclusively by Prism Pharmaceuticals Inc.

The solubilizing agent at the heart of Captisol technology, was invented by Dr. Valentino Stella, a University Distinguished Professor of Pharmaceutical Chemistry, and Dr. Roger Rajewski, director of the Biotechnology Innovation and Optimization Center. The University of Kansas licensed this agent to CyDex, which has led to the development, physical and chemical characterization, formulation development and pharmacokinetic and pharmacodynamic testing. Clinical and safety studies at Guilford and MGI Pharma led to the development of Lusedra.

Eisai Corporation of North America recently announced that the U.S. Food and Drug Administration has approved Lusedra (fospropofol disodium) Injection, an intravenous sedative-hypnotic agent for monitored anesthesia care sedation in adult patients undergoing diagnostic or therapeutic procedures. This drug was invented and tested by University of Kansas researchers before being further developed by the KU startup company ProQuest Pharma Inc. They licensed the drug to Guilford Pharmaceuticals Inc., which was purchased by MGI Pharma Inc. and then the Tokyo-based Eisai.

"The chemical was synthesized in my lab," said Dr. Valentino Stella, a University Distinguished Professor of Pharmaceutical Chemistry.

Lusedra is a proprietary water-soluble prodrug of propofol. Fospropofol was designed by Stella and first created in the lab by Muhammad Safadi, a post-doctoral student of Professor Stella. Former KU professor Dr. Gunda Georg and an associate Dr. Jan Zygmunt, were collaborators in the synthesis of fospropofol. Preclinical development studies were performed at KU in the Center for Drug Delivery Research (CDDR), predecessor of the Biotechnology Innovation and Optimization Center. In CDDR, Drs. Roger Rajewski and Michelle McIntosh led studies including scale-up chemistry development, physical and chemical characterization, formulation development and pharmacokinetic and pharmacodynamic testing. Clinical and safety studies at Guilford and MGI Pharma led to the development of Lusedra.

"We are pleased with the FDA’s decision to approve Lusedra, as it provides a new option for monitored anesthesia care sedation in adult patients," said Cynthia Schwalm, president of Eisai Inc. "With the approval of Lusedra, Eisai continues to fulfill its human health care mission to address the unmet needs of patients."

"It is the first of our products formulated in-house to receive FDA approval ..." - Theron E. Odlaug, Ph.D., CyDex president and chief executive officer

... it provides a new option for monitored anesthesia care sedation in adult patients.

- Cynthia Schwalm, President, Eisai Inc.
KU HTS Lab Instrumentation

Automated liquid handling:
Biomek FX Liquid Handling Workstation
Matrix PlateMate 2X3 integrated with CataLyst-5 Express
WellMate microplate Dispenser
GenesisFE200
MultiDrop 384 Bulk Reagent Dispensers
ELx405 Cell washers
Precision2000
AquaMax DW4
BD Pathway 855 High-Content Bioimager
FujiFilm AP-3000 Label-Free Drug Screening System

Detection Instruments:
The KU HTS Screening facility has several plate readers to read 96-well or 384-well assay plate. All six readers support high-throughput operations, either through stackers or via robotic integration.

Wallac EnVision Multilabel Plate reader
Tecan Safire
Wallac Victor2 V Multilabel Counter
SpectraMax Plus 384 Spectrophotometer
SpectraMax 340PC 384 Spectrophotometer
SpectraMax Gemini XS Spectrofluorometer
GloMax Multi-detection System
xCelligence
Artel Multichannel Verification System
Meso-scale discovery SectorImager 2400

Other Instruments:
ALPS 300 Automated Laboratory Plate Sealer
Covaris L8
XPeel - Automated Plate Seal Removal System
eEMS Incubators/Shaker
Guava EasyCyte Plus system
FPLC for Protein Purification

Imaging Systems:
Nikon Ti-inverted Microscope

Cell Culture Facility:
The cell culture laboratory consists of a quarantine room and a production room, both of which are biosafety level II facilities.

Find more information about the KU HTS Lab or detailed descriptions of available equipment at www.hts.ku.edu.

BD Pathway 855 High-Content Bioimager
Dr. Peter McDonald, HTS research associate, works on a the BD Pathway 855 system, which offers the flexibility needed for high-content imaging of live and fixed cells, enabling versatile solution for live cell and endpoint fluorescence imaging.

KU High Throughput Screening Lab offers more than tech support in new facility
- Information contributed by the KU HTS Lab, TTP LabTech

With the opening last fall of a new facility on the west campus of the University of Kansas, the KU High Throughput Screening (HTS) Laboratory, 2121 Simons Drive, will be able to do more to assist researchers in the drug discovery process.

“A lot of people don’t realize how lucky they are to have this facility here,” said Dr. Rathnam Chaguturu, director of the HTS Lab since 2007.

The KU HTS lab takes a fundamentally different approach to the drug discovery process than HTS labs at other academic institutions by assisting researchers with projects from beginning to end. Lab staff collaborate with researchers to generate workable ideas and provide guidance through each stage of the process to ensure its success. This may involve working with university officials to protect the researcher’s intellectual property rights or the Biotechnology Innovation and Optimization Center to aid in the transfer of results to the marketplace.

The lab’s new 4,500-foot space, located in the Structural Biology Center, provides cancer researchers and others with a wide variety of brand new, cutting-edge equipment to aid in assay development, screening, compound profiling, data mining and more. The presence of the lab at KU strengthens the infrastructure of the KU Cancer Center and brings it a step closer to attaining National Cancer Institute designation as a Comprehensive Cancer Center.

Without the HTS Lab my project would be nowhere.
- Dr. Alexander Beeser, KU Cancer Center researcher

The original KU HTS Lab opened in 2002 as part of the Center for Cancer Experimental Therapeutics (CCET), a project funded by the National Institutes of
Health as part of the KU Cancer Center. Researchers in the Department of Medicinal Chemistry felt their research was becoming esoteric. They needed an HTS lab that would help move research from theory into practical application by translating drug research into action. To do this they needed to be able to study the effect of tens of thousands of compounds on the therapeutic biological target of interest in a short period of time. HTS technology would allow them to do this.

HTS first came into use in the 1980s when a variety of technologies, including the development of high-speed computers, converged. By the 1990s HTS had taken off as an industry. Without an HTS lab a researcher would have to manually place one target compound at a time into a test tube to study its affect on one type of test cell or protein. Imagine doing this 100,000 or 1,000,000 times depending on the size of the chemical library to be screened.

This is impractical because “HTS is like a shotgun approach or roulette,” Chaguturu said.

FDA approves CyDex drug
Captisol technology at center of more new products
(Continued from page 1)

development of new drug products, including Nexterone.

Captisol allowed CyDex to develop a novel formulation of the antiarrhythmic agent amiodarone (originally marketed as Cordarone Intravenous) by increasing water solubility and stability without the cosolvents polysorbate 80 and benzyl alcohol that are used in the innovator product. Cosolvent-free Nexterone addresses the patient care and medication management limitations of conventional intravenous amiodarone in treatment of life-threatening cardiac arrhythmias.

“Prism licensed the worldwide rights to an amiodarone formulation developed with Captisol technology from CyDex in early 2006, and we have worked closely with Prism in providing technical support since then,” said Theron E. Odlaug, Ph.D., CyDex president and chief executive officer. “Along with our technical support, their success in advancing the product to NDA approval in less than three years further demonstrates the value of Captisol technology in developing novel injectable products that enhance patient treatment in the hospital setting. Nexterone’s approval also marks two corporate milestones for CyDex. It is the first of our products formulated in-house to receive FDA approval, and as the fifth product marketed by a CyDex licensing partner, it has the potential to significantly expand our licensing royalty revenue base.”

CyDex and Prism also have been jointly developing a novel Captisol-enabled injectable form of the antiplatelet agent clopidogrel, originally marketed as Plavix, for use in cardiovascular surgery. Clopidogrel is currently available only as an oral therapy. Adding an injectable route for clopidogrel will provide interventional cardiologists more direct control over patient care, and reduce the pre-procedural time required over the oral drug.

“Expanding our Captisol technology licensing business with valued partners such as Prism complements CyDex’s core strategy, which is to develop and market our own line of specialty pharmaceutical injectable products that target unmet needs in intravenous therapy,” said Odlaug. “We are proud to have Prism as one of our expanding group of CyDex licensing partners, and we look forward to successfully completing clinical development of clopidogrel.”

A researcher does not know which type of cells or proteins the target will affect and must test many to see if an interesting target really has the potential for drug development. For instance, a target compound may kill a cancer cell, but if it also kills a regular cell, it is considered promiscuous, and the researcher would not be interested in studying that compound further. Tens or even hundreds of thousands of test compounds must be screened to discover this. HTS automates the process. This means that thousands of compounds can be tested at once. At the KU HTS Lab a researcher can gather information about 100,000 test compounds in a week to 10 days for a cell-based screen or just two to three days for a protein-based screen.

Lab Assistance from A-Z
Expert staff offers project assistance
(Continued from page 2)

Health as part of the KU Cancer Center. Researchers in the Department of Medicinal Chemistry felt their research was becoming esoteric. They needed an HTS lab that would help move research from theory into practical application by translating drug research into action. To do this they needed to be able to study the effect of tens of thousands of compounds on the therapeutic biological target of interest in a short period of time. HTS technology would allow them to do this.

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A resource for scientific discussion
Chaguturu works mainly as a resource for scientists. He encourages anyone to contact him who is seeking ideas

Mosquito
TTP LabTech’s mosquito, available at the KU HTS Lab, provides precise and repeatable nanolitre pipetting, every time irrespective of liquid viscosity or environmental conditions.

(Continued on page 4)
Cutting-edge equipment
All researchers welcome

(Continued from page 3)

for a new project or needs someone with whom to talk through their ideas. He finds that the drug discovery process goes most smoothly when a researcher discusses their ideas with him from the earliest stages of a project’s development. This allows him to provide feedback on how the lab’s equipment can best be integrated into the project to achieve the researcher’s goals and prevents changes from being necessary after work has already been completed. He stresses that everything is done under the researcher’s direction.

“Without the HTS Lab my project would be nowhere,” said Dr. Alexander Beeser, an assistant professor at Kansas State University who was drawn to Kansas by the HTS Lab and the CCET, which funds the projects of junior scientists who are involved in cancer research at Kansas institutions.

“If you want to do HTS, you need access to libraries. As an assistant professor, I could not have purchased one myself, so access to the chemicals was a big advantage. The fact that I controlled my own data, which would not have been possible had I done the screen under the Molecular Libraries Screening Center Network, was also a big plus,” Beeser said.

To inform campus personnel about the services and facilities available at the HTS Lab, Chaguturu tours departments and gives presentations. He helps researchers determine if working with the lab would allow them to reach their goals “better, quicker and faster” than if they used only equipment available through their departments.

Currently, the HTS Lab is almost second to none in terms of detection platforms and for quantifying activity, Chaguturu said.

Even so, they hope to offer more services in the future. They plan to add equipment to handle specific tests to better study such things as neuronal function. In addition, they would like to further automate the equipment by adding robotic capabilities that would allow staff to walk away during testing procedures, which would give them more time to spend with clients.

Three-tiered rate structure

Although the facility operates on a fee-for-service basis, its primary goal is to see that researchers succeed in their research endeavors and are able to transform their work into drug discovery and development projects.

“Charges are flexible, and we will work with researchers to get the mission accomplished,” Chaguturu said.

Unlike most HTS labs run by academic institutions, KU’s lab has an open-service policy and will work with anyone who wants to use the facility whether they are from KU, another university or the pharmaceutical industry.

Charges are flexible, and we will work with researchers to get the mission accomplished.
- Dr. Rathnam Chaguturu, KU HTS Lab director

Researchers have come from as far away as California and Massachusetts to use the lab.

Costs are determined by a three-tiered rate structure. KU and KU Medical Center researchers pay the lowest fees. The fees of researchers from other universities and not-for-profit organizations rest on the second tier. The third tier applies to those from the pharmaceutical industry. Despite the rate structure, all fees are flexible, and researchers with limited funding should feel free to speak with Chaguturu about their HTS needs or to seek guidance on how to best proceed with a project.

For more information about the HTS Lab visit http://www.hts.ku.edu/index.php. To discuss a potential project, contact Dr. Chaguturu at (785) 864-1717 or rathnam@ku.edu.