

SBS/NIH connections

Vanderbilt Center Enables Discovery of a New Generation of Molecular Research Tools

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The Vanderbilt Screening Center for GPCRs, Ion Channels and Transporters (www.vanderbilt.edu/mlscn), in Nashville, TN, is a Molecular Libraries Screening Center Network (MLSCN) facility that has developed out of the Vanderbilt Institute of Chemical Biology's high-throughput screening center. The goal of the Vanderbilt Center, as part of the MLSCN, is to enable eligible investigators from across the world to discover and develop a new generation of small molecule probes to promote advances in our understanding of the structure and function of GPCRs, ion channels, and transporters.

Resources

The Center is committed to providing the resources and infrastructure needed to allow investigators to stay at the forefront of developing novel strategies for modulating some cell surface receptors and transporters, which have proven to be among the most important classes of drug targets. Over the past decades, tremendous effort has been focused on these target classes for the discovery of ligands that interact with the same sites as endogenous ligands or transporter substrates.

However, in recent years, exciting new approaches have developed for regulating these proteins by targeting allosteric sites on the receptors, protein-protein interactions that form signaling complexes, and protein trafficking. The Vanderbilt Screening Center for GPCRs, Ion Channels and Transporters is prepared to discover new tools that act at traditional orthosteric binding sites, and to help move the field forward by exploiting these newer approaches. To accomplish this, it is critical to include measurements of receptor, channel, or transporter functional responses in a whole cell environment, in addition to traditional ligand binding/displacement assays.

Vanderbilt has invested in an HTS infrastructure capable of making measurements using a wide variety of commercially available and novel technologies. The suite of detection modalities within the center includes two Hamamatsu FDSS kinetic imaging plate readers. These readers provide the ability to collect data from all wells of 96 and 384 well plates simultaneously and can add reagents during data acquisition with integrated 96 and 384 well pipetting. Fluorescent data can be collected over wavelengths from UV to far red. Dual excitation, emission and fluorescence polarization modes are up to 10 frames per second.



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Additionally, the FDSS supports ultra low-light detection for aequorin and other kinetic/flash luminescence formats. This combination of capabilities provides tremendous flexibility for measuring kinetic responses from a test compound's actions on a wide range of membrane proteins.

For assays demanding a higher degree of spatial resolution, the Vanderbilt facility incorporates the BlueShift Biotech Isocyte plate cytometer. This laser scanning device provides two laser excitations (442 nm and 488 nm) and up to four simultaneous emission channels that may be used for standard fluorescence and fluorescence polarization measurements at spatial resolutions as high as 1 micrometer. The Isocyte thus has utility for a variety of cell-based and cell-free (including bead-based) assays requiring a high degree of spatial resolution.

Together with fully-automated and time-locked robotic scheduling and state-of-the-art liquid handling, including the Labcyte Echo550 acoustic compound reformatter, the Vanderbilt facility is positioned to provide for the most demanding, non-homogenous live-cell, fixed-cell, and cell-free assay protocols.

Organization

The authors are co-principal investigators of the Vanderbilt MLSCN facility. Both have extensive academic and industry drug-discovery backgrounds that include using HTS to discover tools to study GPCRs, ion channels, and transporters. While both investigators have experience in working with all three major protein classes that receive focused attention at the Vanderbilt site, Dr. Conn has particular expertise in membrane neurotransmitter receptors and has been at the forefront of recent advances in the discovery of novel allosteric ligands for this receptor class. Dr. Weaver has been a pioneer in developing novel technologies for assays of ion channels and transporter proteins. Together, they are responsible for defining and directing the overall strategy for the center.

The Vanderbilt Center is divided into three cores: biology, chemistry, and technologies (automation and informatics). The biology core—which combines assay development, validation, HTS implementation—is led by Michelle Lewis, PhD. Dr. Lewis has extensive experience in designing, validating, and implementing HTS in drug discovery settings. She is supported by a staff of two full-time biologists, Debbie Mi, PhD, and Kate Lomsen. Together, the biology core works with investigators funded through the NIH's X01 program to adapt their assays to the Vanderbilt facility's screening systems and then to run these assays to discover modulators within the MLSCN's compound collection.

The chemistry core director is Gary Sulikowski, PhD. Dr. Sulikowski is a renowned synthetic organic chemist. The core's functional manager is Darren Orton, PhD, who has extensive experience in performing rapid hit-to-lead and SAR studies as part of pharmaceutical drug discovery. Dr. Orton is joined by Richard Williams, PhD, who has extensive experience with rapid hit-to-lead work using parallel synthetic techniques. The chemistry, biology, and informatics cores work together to turn promising hits from HTS into chemical probes.

The technologies core, responsible for laboratory automation and informatics, is directed by Cheryl Austin, who has a broad background in laboratory automation and database management. The automation and informatics team also includes programmer Michael Williams and systems administrator Beth Kurowski. This team plays a dual role, working with both the biology and chemistry cores to establish and maintain automation and a data management infrastructure compatible with the widest variety of technologies to enable tool discovery for GPCRs, ion channels, and transporters.

Core members meet regularly to plan strategies and align resources to ensure that the center functions smoothly and efficiently to fuel the advancement of scientific knowledge and understanding through the development of the next generation of tools. For more information, e-mail: david.weaver@vanderbilt.edu.

2007 Conference

Whereas the 2006 program took on a chemistry theme, the 2007 conference will carry a different biological theme in order to attract the same number and quality of abstracts for the scientific program and ensure vendor support, given that this meeting will be held only seven months after the 2006 meeting. As of 2007, the annual conference date will move permanently from September to April. It is essential that we make everyone aware of this change, and you will begin to receive notices from the SBS office about it and see notices on the SBS website (www.sbsonline.org).

The 2007 annual meeting, our first April conference, will be held in Montreal, Quebec, Canada. Therefore, the SBS staff is now organizing two annual conferences simultaneously. This is not an easy task, but they are ready for the challenge.

The 2007 meeting will also see an expansion of the scientific program. There will be two drugdiscovery-related sessions organized in cooperation with two allied organizations. One will be a session on toxicology organized by scientists from the National Toxicology Program (NTP) and the Environmental Protection Agency (EPA). These are two US government agencies that are looking into high-throughput toxicology testing methods. This will give a venue for the exchange of techniques and technologies for toxicology testing, which is of interest to pharmaceutical and academic scientists as well.

A second session is being organized with the International Society for Analytical Cytometry (ISAC). ISAC, which includes members from pharmaceutical companies as well as academic and gov-

ernment organizations, focuses on cell-based techniques that include flow cytometry and high-content screening. The organization holds an annual meeting every other year. This year it is in Quebec City, Quebec, Canada, May 22-25 (see www.isac-net.org). We look forward to a successful collaboration with them.

Europe

Another strategy change will occur with the rotation of the annual conference. The amount of work that will go into organizing two annual conferences so close together, and the more complicated logistics of planning a European meeting in 2008, were carefully considered. It was decided to hold the 2008 conference in the USA (site yet to be determined). The one-time doubling up of conferences, coupled with a desire to have a more frequent presence in Europe, supports a new strategy to hold a regional meeting in Europe every year that the annual conference is in the USA. Our first European regional meeting is slated to take place in the fall of 2007 with LRIG-UK, and we are currently looking for a suitable site for a regional European meeting in 2008. Sites for future European annual conferences are being evaluated. In the meantime, if you have any questions or comments, I welcome your input. Please e-mail: kolb_a@msn.com.

As our new name implies, we are a Society of Biomolecular Sciences that includes high-throughput screening. New programs and collaborations are being developed that will be discussed in forthcoming issues of *SBS News*.