HIGH-THROUGHPUT SCREENING AND DRUG DISCOVERY AT ST. JUDE CHILDREN'S RESEARCH HOSPITAL

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We highlight the role of the HTS Core Facility at St. Jude Children's Research Hospital in Memphis, TN, USA. This facility has a significant focus on discovering and developing new chemical entities based on an extensive, on-site chemical library.

Introduction

In the past decade high-throughput screening (HTS) has been used predominantly in the pharmaceutical and biotechnology industries for drug discovery. That landscape has changed greatly in recent years. Government institutions, universities and hospitals have established a variety of screening centers with somewhat mixed objectives including identifying probes that can be accessed by the public, identifying drug leads for potential licensing opportunities and providing contract services for pharmaceutical companies (1–3). Furthermore, HTS also has expanded to emerging markets where unique collections of compounds or extracts, such as traditional Chinese herbal medicines, are used (4).

In this article we highlight the HTS Core Facility at St. Jude Children's Research Hospital in Memphis, Tennessee, USA. St. Jude Children's Research Hospital was founded in 1962 by the late entertainer Danny Thomas to "advance cures, and means of prevention, for pediatric catastrophic diseases through research and treatment" (5). At St. Jude, no child is denied treatment on the basis of race or religion, and no family ever receives a bill from St. Jude for their child's treatment. St. Jude handles all costs not covered by insurance and total treatment cost for patients with no insurance.

The hospital's vision to be the world leader in advancing the treatment and prevention of catastrophic diseases in children is developed through excellence in patient care and through strong programs in basic, translational and clinical medicine. The HTS Core Facility is part of the Department of Chemical Biology and Therapeutics, which works, together with other St. Jude research faculty, to discover and develop new chemical entities that increase understanding of the pathophysiology of catastrophic pediatric diseases or that function as therapeutic leads for the treatment of such diseases.

Supporting Translational Research: The Roles and Goals of the HTS Core Facility

The HTS Core Facility at St. Jude was established in 2006. The facility at St. Jude uses both commercially available chemical libraries and St. Jude's own repository of chemical compounds designed by chemists in the Department of Chemical Biology and Therapeutics for probe development and drug discovery. St. Jude has the capacity to house 1 million chemical compounds on site.

The staff of the HTS Core Facility collaborate with research faculty at St. Jude to develop assays, validate them and miniaturize the assays so that they are amenable to automation. After a screening assay is successfully

The campus of St. Jude Children's Research Hospital in Memphis, Tennessee, USA (photo credit: St. Jude Biomedical Communications).

developed, the facility conducts the screening experiments using the assay and executes the appropriate secondary and ADME/Tox screening to assist in determining mechanism of action, physical properties and off-target toxicities of any compound "hits" from the primary screen.

In addition to conducting screening projects in collaboration with St. Jude research faculty, the HTS staff manage the compound store and evaluate and develop novel drug discovery technologies.

Creating A State-of-the-Art HTS Facility

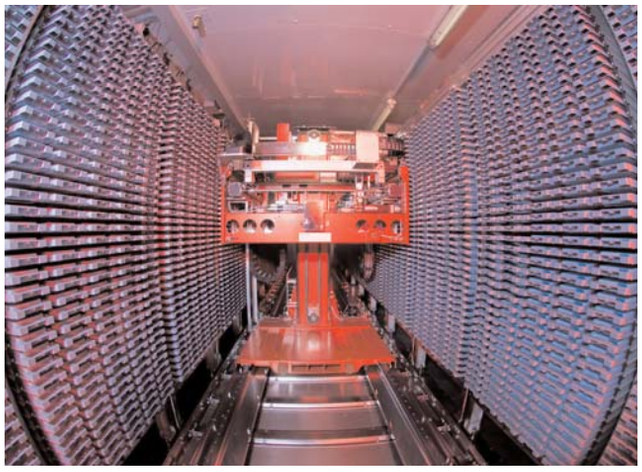
The HTS Core Facility at St. Jude employs state-of-the-art automation and assay technologies. The facility is located in the Integrated Research Center. The facility can perform biochemical and cell-based (BSL2+ compliant) assays using an on-site library of 525,000 compounds and full siRNA sets for mouse and human genomes that are stored in a REMP-designed automated compound store with the capacity to store 1 million compounds or other materials (e.g., RNAi molecules).

The facility has multiple integrated screening robots that contain various liquid-handlers and high-throughput plate readers for a variety of assay outputs including Alphascreen®, fluorescence intensity, fluorescence polarization, time-resolved fluorescence, luminescence, and absorbance. The facility also has an automated microscope and flow cytometer for cell-based high-content screening.

The robots include Staubli robotic arms for moving multiwell plates from station to station; Liconic incubators, each with a capacity of up to 242 plates, which can be swapped among different docking stations during the run process; and scheduling software that controls the screening system operation and handles the deposition of all screening-relevant data.

Progress in HTS Research

Since its inception in 2006, the HTS facility has initiated multiple HTS projects. The work from the screening center and the Department of Chemical Biology and Therapeutics at St. Jude is already beginning to appear in the literature (6–9). The HTS center also is undertaking new technology initiatives including screens involving RNAi.



The Chemical Library Storage and Retrieval Facility in the HTS Core Facility. St. Jude Children's Research Hospital can store up to 1 million chemical compounds or small molecules (photo credit: St. Jude Biomedical Communications).

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