The BioPhenics High-Content Screening Platform

Call for Projects 2013-2014

"High-Throughput Cancer Research Screening"

HiCanScreen

The BioPhenics High-Content Screening Center launches the call *"High-Throughput Cell Biology for Cancer Research: from screening to applications"* supported by the Paris Alliance of Cancer Research Institutes - PACRI. This call aims to support research groups throughout Ile-de-France working on cancer-related cell models for target validation or/and drug repositioning. Research groups will receive financial and technological support in their needs of image-based High Content and High Throughput Screening of chemical and siRNA libraries.

Submission deadline is February 1st, 2014 (midnight).

A- Overview of Principles and Processes

Phenotypic analysis is an essential fundamental concept in traditional and modern biology and pharmacology: a cell or organism is perturbed, for example, by genetic mutation (naturally occurring or induced) or by small-molecule treatment, changes in phenotype are observed, and conclusions are then drawn about the mechanisms underlying the biology. Phenotypic screens are also key in providing tools to study entire signaling pathways or networks.

Automated microscopy, image analysis, and informatics have become robust enough to allow "automated cell biology" to be one of the most powerful methods to address the challenges of fundamental and applied cell biology in the *–omics* era. The level or granularity obtained by automated microscopy and the capacity to track multiple features of cells (signaling pathways, morphological characteristics of small intracellular objects, and dynamic behavior of cells and sub-cellular compartments, etc.) lead to the concept of High Content Screening (HCS), where several dozen parameters are acquired for each cell to measure the effect of perturbators (siRNAs and chemicals). The entire chain of discovery, from basic knowledge to chemical lead identification, is potentially affected by these new tools.

The BioPhenics screening center is a cell-based phenotypic analysis facility that has been established at the *Institut Curie* to accomplish two major goals: (1) discover small molecules and molecular pathways that impacts biology and medicine; and (2) innovate the process through which new molecular pathways, probes and drugs are discovered using cellular models.

Through this call, BioPhenics will offer researchers the opportunity to conduct cell-based screens, using comprehensive or dedicated siRNA or chemical compound libraries available in-house, in association with cancer-related cellular models. Cell phenotypic modifications are detected and quantified on the platform using transmitted light microscopy-based assays.

B - Eligibility and project evaluation criteria

The principal investigator of the project must belong to a research team, affiliated to academia and/or to the public health sector located in Ile-de-France. Screening projects will be selected by a scientific advisory board based on its feasibility and scientific relevance in the cancer field.

C – Financial Support

The BioPhenics platform, through its PACRI grant, will provide financial support for a maximal of 80% of the cost of the screening. Please note that it is very difficult to estimate the total cost of a screening campaign until a number of factors are known. This includes, but is not limited to:

- How much HTS/HCS method development and validation is required
- The complexity of the assay (number of manipulations, difficulty of data analysis)
- Number of compounds or libraries screened
- Data handling and storage

Typical cost for screening a 1,000 molecule library using 2 antibody-based staining is around 6,500 Euros. A siRNA library of 500 siRNAs (125 genes, 4 siRNAs/gene) in the same conditions typically costs 5,700 Euros.

D – Compound Collection and siRNA Libraries available

Investigators have access to several siRNA libraries and compound collections already own by the BioPhenics laboratory.

- **Approved drugs and compounds of known bioactive and clinical properties.** There has been a recent flurry of activity in the "repurposing" of known drugs, which allows for rapid translation from screening hits to the clinic. These compound sets are also excellent tools for revealing valuable pharmacological insight into new targets.
    - **NCI-DTP Approved Oncology Drugs Set [89 compounds]:** Primarily chemotherapeutic agents and some target-based (kinase) inhibitors. Mechanisms include antifolates, DNA damage agents, kinase inhibitors, and inducers of apoptosis. This library is appropriate for testing phenotypic cellular assays for the involvement of pathways of cell signaling and metabolism. These potent compounds may have additional unknown activities useful for cancer chemotherapy.
    - **Enzo Collection [800 compounds]:** Includes FDA-approved drugs (640), Protease inhibitors (53), Phosphatase inhibitors (33), Kinase inhibitors (80)
    - **Prestwick 100% FDA approved drugs [1200 compounds]:** Presents the greatest possible degree of drug-likeliness.

- **Diversity sets**

    - **NCI Natural Products Set II [120 compounds]:** This small collection consists of natural products derived from plants and microbes. The primary application of this library is cancer research, as the compounds were selected by the NCI to inhibit the proliferation or survival of mammalian cells. While many of the compounds are widely used, with extensive mechanistic information available in the scientific literature, others have biological mechanisms that remain to be elucidated.
    - **NCI Mechanistic Set [879 compounds]:** This small collection of diverse compounds is a good choice for early screening efforts on a small scale. Based on distinct patterns of growth inhibition for cancer cell lines, these compounds have the potential to reveal pathways important for different types of cancer, but may also be useful for discovering small molecules with novel activity, and interrogating signaling pathways in eukaryotic cells. National Cancer Institute
    - **NCI Diversity Set II [2000 compounds]:** This collection of structurally diverse compounds was developed by the Developmental Therapeutics Program at the NIH/NCI from compounds in their repository of 140,000 compounds. Most of the compounds in this library are relatively rigid, with 5 or fewer rotatable bonds, having a tendency to be planar, 1 or less chiral centers, and pharmacologically desirable features (i.e., they are not electrophilic, unstable, organometallic,

polycyclic aromatic hydrocarbons, etc.). Many of these compounds would not pass the rigorous filters used in current compound library design, but they offer a tremendous diversity in chemical space.

***Larger libraries*: Note that screening of larger libraries is expensive and time consuming. In case this option is retained, a previous discussion will be necessary to estimate the best library to be screened and the associated costs.**

- **siRNA Libraries.** Several small collections of arrayed siRNA library plates were designated to facilitate your screen project. The below plate numbers are for 384-well plates. Screeners using 96-well plates for their assay will be provided with the appropriate information to translate 384-well plate numbers to 96-well plate numbers for the purposes of labeling assay plates. Some exemples of siRNA libraries available are described below.

Library name (human collections)	N° of genes	N° of siRNAs	N° of 384-well plates
Small GTPases	147	588	2
Kinesins	51	204	1
VATPases, ESCRTs, SNAREs, Exocyst, Golgins	154	616	2
Kinases	685	2740	10
Reduced Kinome collection	573	2292	4

E – Publication policy

Co-authorship between BioPhenics and the supported laboratory will be the rule. Depending on the technical investment several people may be proposed to be co-authors in the publication.

F – Proposal submission and schedule of the call

Proposals will be selected by a scientific committee, composed of members of the Scientific Advisory Board.

Submission deadline is February 1st, 2014 (midnight).

Proposals must be sent by email to: bfx-screening@curie.fr, using the attached HiCanScreen form.
All proposals must also be sent by post mail (one signed paper copy) to:

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