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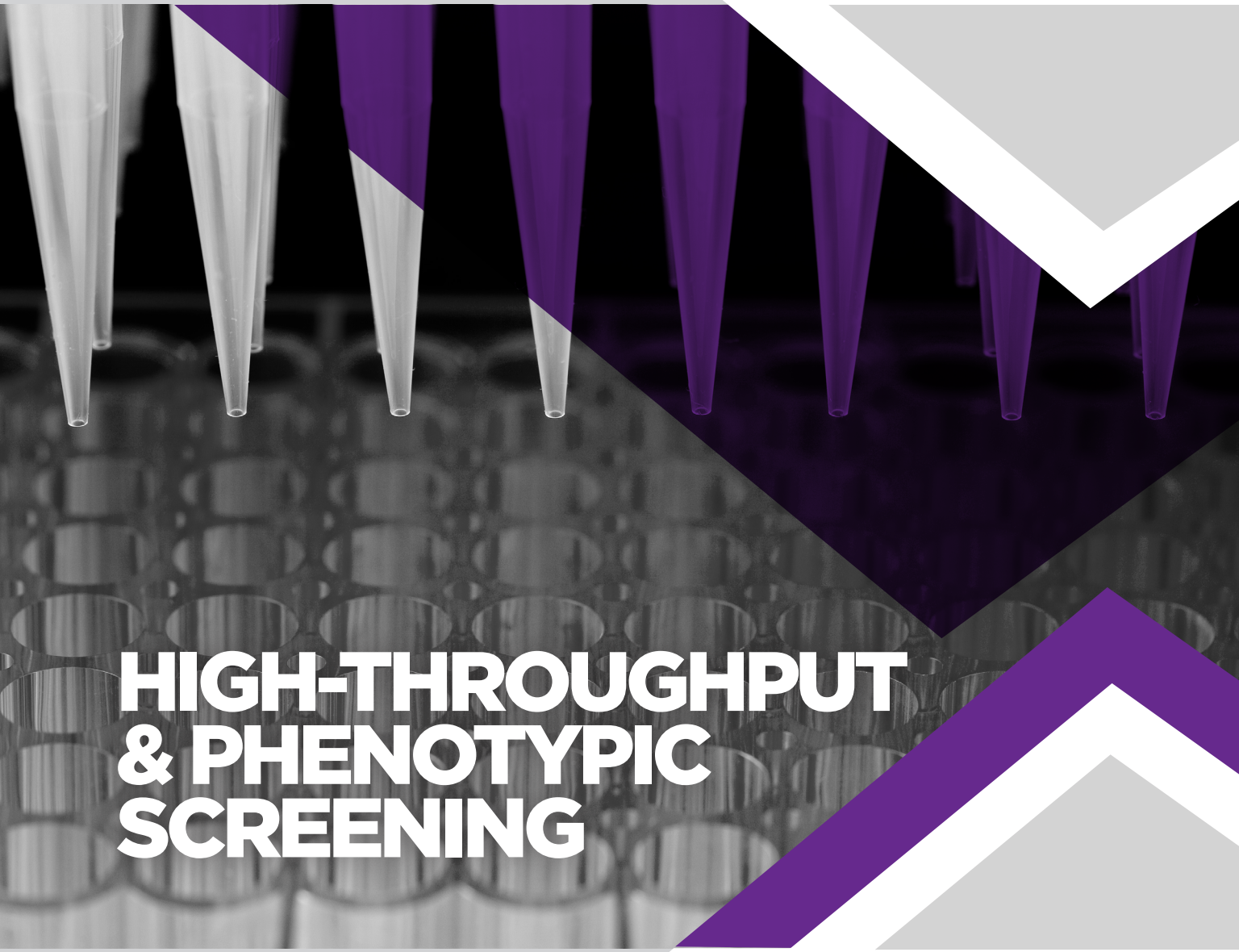

HIGH-THROUGHPUT & PHENOTYPIC SCREENING

Imaging and detection systems, automation, informatics, and assays and reagents for high-throughput and phenotypic screening – together, they spell *discovery*.

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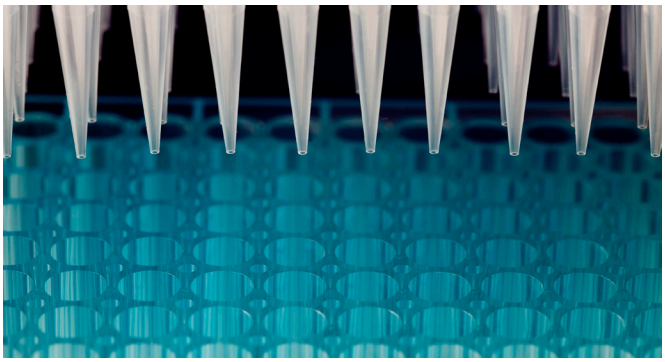
I Screen. You Screen. We all Screen... but How?



In the world of Drug Discovery, screening is an essential method for analyzing a group of chemical entities, small or large molecules, or compounds for a particular function in a prescribed assay. Real advances in screening technologies – both reagents and instrumentation – are occurring on a larger scale in biotechnology and pharmaceutical companies. Companies like these have enormous proprietary libraries that they interrogate on a daily basis in the search for the next blockbuster drug.

Two of the most common types of screens are high-throughput screens and phenotypic screens. Keep reading to learn what sets them apart!

High-Throughput Screening Tackling Targets: 96, 384, 1536, or 3456 at a time

High-throughput screening, commonly abbreviated as HTS, is at the core of many biopharmaceutical discovery programs. It enables the interrogation of a panel of chemical structures and their physical association with the screen's protein target. This approach is known as forward drug discovery.

The goal of a broad screening assay like this is to weed out the hundreds, thousands, or hundreds-of-thousands of chemicals that do not bind with or impact the activity of the target. Even with properly selected libraries, the rate of identifying hits can can often be below 1 %, reflecting the importance of large, well-characterized libraries.

HTS is made faster and, therefore, more powerful through the addition of robotics and automation. High-density microplates such as 1536-well library plates can be quickly and accurately replicated, the target added simultaneously, and the plates moved seamlessly to the adjacent plate reader with smart robotics. This process can continue 24 hours a day, seven days a week, without the need for human intervention. From there, the hits move on to secondary screening, where hits turn into leads.

Phenotypic Screening Tracking Morphology, Viability, and Interactions – Oh my!

HTS campaigns involving purified recombinant targets, once preferred by biopharma, is now giving way to phenotypic screening. Phenotypic screening enables analysis of cellular responses within a complex, cell-based system, rather than in a minimalist, biochemical setting, like traditional HTS. This approach is also known as forward drug discovery.

A cell phenotype can provide valuable information about how your target cell or tissue responds to a specific treatment. Does it induce an upregulation in mRNA synthesis? How does it impact key behaviors like autophagy and exocytosis? By tracking one or several parameters of a cell's phenotype after treatment, it's possible to extrapolate the in vivo effects.

Unlike HTS which often relies on numerical signal readouts, phenotypic screening requires the capacity for imaging. This requirement brings with it a few restrictions, including that experiments must be conducted in sterile, atmosphere-controlled environments with adequate room for cell growth, migration, and interaction. 96-well plates are a common format for these assays.

With the right hardware and software, and a good sense of which cellular events you're trying to capture, phenotypic screening can be as automated as high throughput. Still, the assays take longer than traditional HTS assays because they assess a complex biological response to a compound challenge.

THE MOLECULAR HAYSTACK

Take control of your molecular haystack and find meaningful associations faster and with less hands-on time. With high-throughput screening (HTS) and phenotypic screening, you can tailor your process and find more meaningful matches in even the deepest haystacks.

PHENOTYPIC SCREENING

Forward Drug Screening

HIGH-THROUGHPUT SCREENING

Forward Drug Screening

1

BASIC BIOLOGY:
What are the general characteristics of your disease process?

IDENTIFY YOUR TARGET:
What targets have been flagged by data mining and in silico approaches?

2

PHENOTYPE(S) SELECTION:
Which phenotype(s) will indicate that a candidate is hitting the right pathway(s)?

VALIDATE YOUR TARGET:
Does your target stand up to validation in silencing or blocking assays?

3

THE SETUP:
Have you chosen the right cells, culture system, and analysis method? Are your reagents ready?

SHH! IT'S A LIBRARY:
Which library is best suited to your target? (Hint: Think about target constraints, like pH or temperature) Are you interested in small molecules, large molecules, or fragments?

4

READY, SEED, DOSE, RUN:
Watch 'em grow! Is your assay automatable? (Hint: Yes! It is!)

THE GREATEST HITS:
How many compounds will you need to screen? (Hint: Expect a hit rate below 1 %)

5

ANALYZE PHENOTYPE(S):
Will you grade your phenotypes by microscope or plate reader? (Hint: That depends on your throughput!)

CONFIRM YOUR HITS:
Are your hits still active after you check them across a concentration range?

6

OPTIMIZE:
Can you improve your candidate's profile with iterative rounds of medicinal chemistry?

OPTIMIZE:
Can you improve your candidate's profile with iterative rounds of medicinal chemistry? (Hint: This could include solubility, activity, or stability)

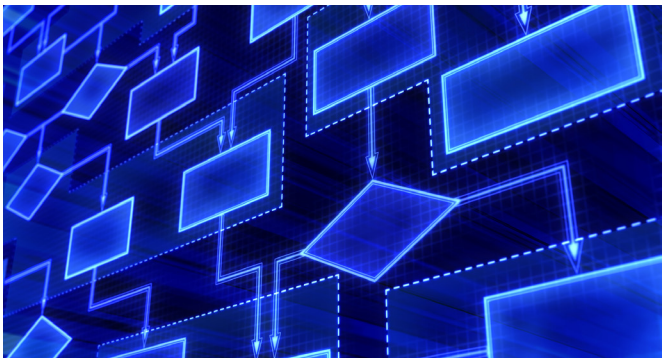
7

TRY TO IDENTIFY YOUR TARGET:
Will your target identification efforts succeed? (Hint: Not all drugs have known targets.)

BASIC BIOLOGY:
Does your putative therapeutic work in a complex system, like organoid culture or an animal model?

These two complementary approaches will likely arrive at different drugs for different diseases. One is not better than the other, rather they serve different purposes. Choosing the right option for your screening campaign could put you ahead of the curve!

Advances in HTS: New Targets, New Technologies, and Newer Workflows



Target-based high-throughput screening (HTS) has been the foundation of biopharma's drug-discovery efforts over the past 20 years, but several advances have emerged to change the face of HTS for the better. These advances run the gamut from tweaked targets, more powerful technologies, and thinking differently about the HTS workflow, but the one thing they all have in common is that they are making HTS less of a random search for matches and more of an informed, intelligent process. Keep reading to learn about a few of the advances.

Scientist, Know Thy Target:

This first advance isn't necessarily new, but it has definitely shaped the typical HTS workflow over the recent past. In the heyday of HTS, all targets were treated the same. Kinases were treated like GPCRs. Phosphatases were treated like nuclear hormone receptors. They were all subjected to the same scattershot HTS approach, being introduced to enormous therapeutic libraries until some interacted in a favorable way. This approach required significant investment in time and resources, but still resulted in the identification of a number of successful lead compounds.

By characterizing the biophysical properties of the compounds in a library, those compounds can be grouped into rational subsets. Now that we can confidently identify and group proteins by their function, targets with specific requirements (pH, temperature, etc.) can inform which library subsets should be screened, saving not only time but also valuable microliters of library. Beyond smart library subsets, computer-based in silico screening has gained traction by bringing the first round of screening to the cloud. The search for potential binding partners can now occur in virtual space!

Even Higher Throughput Screening?

What's higher throughput than high throughput? Super-high throughput? Mega-high throughput? Ultra-high throughput? Yes. Ultra-high throughput screening (uHTS) is the next generation of HTS, in which the liquid handling is conducted via a precise dispense of minimalist volumes of reagents into microreservoir plates. Fast dispense of low reagent volume can be achieved using acoustic droplet ejection (ADE). This technology enables the use of low reagent volumes (nL to µL volumes) with high reproducibility.[1]

Fragment-based Lead Discovery (FBLD)

Turning HTS on its head, FBLD eschews larger, complete drug-like compounds in favor of small (250 – 350 Da or < 20 nonhydrogen atoms) fragments. When screening a compendium of fragments, the goal is to find bits and pieces that fit within the target's binding pocket. Of course, these smaller, incomplete fragments don't form tight associations with their target proteins, so the fragments receive significant attention from medicinal chemists once fragment hits are identified – the goal is to build the potential drug from the binding domain up.[2, 3]

Microfluidics for the Masses

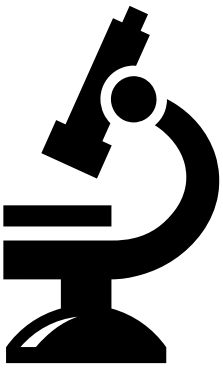
For smaller labs or do-it-yourselfers, investing in expensive platforms may not be realistic, but – luckily enough – a group of engineers have put forth the specs to build your own microfluidics platform for medium- to high-throughput screening. The resulting platform doesn't require any pumps or vacuums, which helps to shrink the footprint and cost of the technology.[4]

If the thought of building a microfluidics platform from scratch is out of reach, don't fret; consider outsourcing your project to an experienced contract-research organization (CRO). They have the knowledge and technical resources to make your screening campaign a reality.

References:

1. T.D. Dawes et al., "Compound transfer by acoustic droplet ejection promotes quality and efficiency in ultra-high-throughput screening campaigns," *J. Lab. Autom.*, 21:54–75, 2016.
2. M. Baker, "Fragment-based lead discovery grows up," *Nat. Revs. Drug Discov.*, 12:5–7, 2013.
3. D.A. Erlanson et al., "Twenty years on: the impact of fragments on drug discovery," *Nat. Revs. Drug Discov.*, 15:605–619, 2016.
4. Z. Chen et al., "Arbitrarily accessible 3-D microfluidic device for combinatorial high-throughput drug screening," *Sensors*, 16:1616, 2016.

Advances in Phenotypic Screening: Seeing is Believing



You may be wondering, "If target-based HTS is so great, why bother with phenotypic screening?" Well, for HTS's many strengths, it has one large and costly weakness. Since target-based screening is focused on identifying small molecules or biologics that interact with one specific target, oftentimes hits and leads that seem promising in pharmacokinetic studies produce disappointing results once tested into a complex system (e.g., 2-D or 3-D cell culture, organoid culture, animals). Phenotypic screening can help to avoid nasty surprises like these because the screening starts in a complex system, and works towards identifying a target, and not the other way around.

With all the buzz surrounding phenotypic screening, you'd think it is a revolutionary new concept. In fact, phenotypic screening was one of the original approaches for testing compounds for therapeutic activity by monitoring cells' response to treatment. Only after a promising effect was seen would efforts be made to identify the drug's target (rational drug design). As HTS grew in popularity due to its industriability and automation-friendly workflows, the more labor-intensive phenotypic screening fell in prominence, but that's all changing with today's improved cell-analysis techniques and target identification methods. Keep reading to see how phenotypic screening is poised for a comeback!

High-Content Analysis (HCA):

Smarter imaging devices are making phenotypic screening simpler and less time intensive to conduct in the laboratory. Instead of screening cultures for a single phenotype or marker, HCA generates more information in roughly the same amount of imaging time and with no additional hands-on time. HCA requires advanced, plate-based imaging equipment and sufficient analytical power to make sense of the panel of information, but it is no more complex for the end user than screening for a single marker. HCA is making phenotypic screening even more powerful.

Turn the Volume Down:

Culture systems, whether they be cell culture, cell coculture, or tissue culture, all have one thing in common. They must all keep the cultures physiologically stable by controlling the temperature, gas exchange, and nutrient availability. Typical 96-well plates have drawbacks, including evaporation, uneven fluid distribution, and the sheer volumes of media and other reagents required. New options for phenotypic screening have miniaturized the 96-well plate with each well being replaced by a mere drop. Within that drop, cells have the space to grow and associate, but don't require the same footprint or volume of media.

The Differentiator:

Induced pluripotent stem cells (iPSCs) have enabled phenotypic screening across a striking variety of cell types all derived from fully differentiated tissue samples. One small punch biopsy full of fibroblasts can be dedifferentiated into stem cells and then redifferentiated into the most biologically relevant cells. This makes it possible to evaluate the influence of a cell's genome (and, to a lesser extent, its epigenome) on cellular behavior, health, and response to a screening library. This specificity and adaptability make phenotypic screening of iPSCs more flexible and useful than ever before.

YOUR HOTTEST TARGETS ARE OUR NEWEST ASSAYS

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