Technology innovation will help prepare drug discovery for smart screening era

Drug discovery is undergoing a transformation powered by advances that provide more knowledge from biological assays, allow for screening orders of magnitude more molecules and enable smarter selection of compounds.

By Dr Clive Green and Dr Philip Spencer

We are on the cusp of having previously unimaginable amounts of information about each target and many more targets to prosecute. For instance, last year AstraZeneca launched an integrated genomics initiative through which scientists will investigate data from as many as two million human genomes, including more than 500,000 from clinical trials run by the company[1].

This possibility of being able to interrogate many more targets, and learning more about the features that drive compound identification and optimisation, is a major step towards the ability to intelligently select compounds to screen in drug projects. The diversity screening commonly performed in pharma workflows today – those all-by-all screens, necessitated by our lack of knowledge about targets and compounds alike – could and should be replaced by smart screening of targets with just the compounds deemed the most promising fits by strong scientific evidence. This would allow researchers to be more judicious about the use of samples, rather than wasting a proportion of each compound for every new screen, despite the low likelihood of most being effective.

Smarter screening approaches would ease the pressure on compound libraries in pharma, biotech and academia[2]. Currently, the 'broad brush' method of screening requires having large volumes of compound samples on hand at all times; these samples often have to be shuttled between lab facilities, sometimes around the globe. Each diversity screen chips away at the volume remaining in the library, raising concerns that precious samples will be exhausted in routine screening and then unavailable when truly needed.

Innovative automation can help alleviate this challenge and preserve compounds for the coming era of smart screening. At AstraZeneca, a collaboration with several vendors in compound storage and processing is allowing us to rethink our compound library usage and approach. By pushing the boundaries for automation, labware and software, we have made it possible to extract more value from each compound in readiness for an increase in new targets. This approach could serve as a template for other organisations looking to extend their own capabilities. We recognise the need for innovative automation solutions across many areas of drug discovery, and collaborations with academia

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and vendors will be an important element in delivering scientific impact from these investments.

Opportunity

As drug discovery scientists generate new biological screening data about a host of targets, there is a pressing need to improve the management of compounds. Since no company has unlimited access to compounds, ensuring that the available samples last as long as possible is essential for safeguarding the success of future screens when new targets emerge.

The challenged that faced us – one that will be familiar to any scientist involved in drug discovery – was increasing our capacity for high-throughput screening without depleting our compound library. AstraZeneca has more than two million compounds at its disposal, with approximately 150,000 at risk of depletion, and a cost of replacement of $50 to $100 per compound. At the same time, we continue to seek new collaborations with academic institutions and other external organisations. Each new project increases the number of high-throughput screening campaigns we would like to run.

Addressing this challenge involved several separate technical goals. In order to achieve the aspiration of being able to select any compound for any screen we needed more rapid automated storage and retrieval capabilities. Miniaturisation was also necessary to make each compound last for many more screens. Ideally, scientists at the company's major research hubs would have local access to key compounds, rather than having to request them from a central facility and have them shipped. That would require a different approach to store more samples in the same equipment footprint and conserve sample volumes across multiple locations.

These were not trivial tasks. If they could be accomplished, though, it would result in workflows that would be much more amenable to the kind of smart screening we hope to deploy.

Technical approach

We recognised that a complex project like this could not be solved by a single technology platform or vendor. We approached vendors with whom we had established long-standing relationships for compound storage and retrieval (Brooks Life Sciences), liquid handling (Labcyte) and IT systems (Titian Software) and addressed the challenge together. In addition to having the vendors work closely with AstraZeneca during this project, it was essential that they also worked in partnership so that any solutions would be integrated and fully automated, without the pitfalls of incompatible software or hardware, or requiring manual intervention to go from one platform to another.

In one major step, we transitioned the liquid handling approach toward trays of tubes, rather than traditional microplates. This required our liquid handling vendor to work hand-in-glove with our tube manufacturer, crafting specialised tubes compatible not only with the compound storage infrastructure but also with the acoustic dispensing

liquid handlers where they would ultimately be used. These innovations also led to a dramatic increase in the number of tubes that could be held in a tray and a new barcoding system for meticulous sample tracking.

Integrating software was also important. Our IT systems vendor teamed up with us and the other vendors to develop a software solution that could manage the entire process including sample ordering, automated storage and retrieval, and the liquid handler protocols for screening. It also reports process results, such as compound quality and location, plate barcodes and inventory data.

To break through what has been a technological barrier for acoustic liquid handling, our liquid handling vendor developed a novel platform with innovative hardware and software features to support the transfer of samples from storage tubes. Additionally, it developed a complementary robotic platform to seamlessly integrate its acoustic liquid handler with tube- and microplate-handling devices in one modular system for a streamlined and contained process optimised for maximum throughput and efficiency.

Technology development and validation for this completely novel approach has taken two years, and we will start to deploy this new solution at AstraZeneca this year.

New capabilities

The improvements from this new integrated approach will be significant. According to our models, the workflow will be able to support more than 70 high-throughput screening campaigns each year, a sizable increase from our previous approach. Automated storage and retrieval capacity will increase four-fold from 20,000 to 80,000 samples per day and using high-density trays that each hold 1,280 acoustic dispensing tubes will enable 100,000 samples to be plated in just 30 hours for a typical primary screening campaign.

By creating a completely non-contact workflow using solely acoustic dispensing liquid handlers, rather than the current industry standard, a hybrid of contact and non-contact dispensing, we anticipate a 10-fold reduction in sample volume across all assays[3,4]. The fully-acoustic solution, with its groundbreaking acoustic tube design and innovative acoustic liquid handling technology, will streamline many processes and reduce the number of steps needed within compound management to generate plates for screening. For an organisation that runs as many assays as AstraZeneca, that represents significant cost savings.

By increasing compound access at our major research hubs, each site will hold the most relevant section of the company's library for its scientific requirements. Each site will have lower volumes of each sample, but because of the miniaturisation made possible by acoustic dispensing technology, those samples will last much longer. The risk to our 150,000 endangered compounds, for example, has been completely removed. Indeed, this shift would not have been possible without such a degree of miniaturisation; there is simply not enough building space at some of our sites to store as many as one million compounds in the volumes that would otherwise be needed for so many screens.

High-density storage trays holding sample tubes compatible with acoustic liquid handling

Automated storage and retrieval capacity will increase to 80,000 samples per day. Thanks to high-density trays that hold 1,280 acoustic dispensing tubes apiece, it will be possible to plate 100,000 samples in just 30 hours

Together, these advances will contribute to significant business impact. An extensive cost analysis determined that the total cost of ownership for this new system – with its dramatically higher throughput – is actually lower than the cost of the previous system at AstraZeneca. Other analyses have shown that the new approach will improve the overall quality of screening data generated, giving our scientists a better foundation for their studies.

Vendor collaborations

Despite the prevalence of laboratory technologies in drug discovery, there remain areas where innovation and investment in automation could offer real benefit to productivity and quality[5]. In chemistry, for instance, there remains a predominance of manual handling activities – a situation that could be transformed with the kind of liquid handling automation and miniaturisation implemented in the high-throughput screening process. At AstraZeneca scientists are currently developing automated systems for many of the common chemistry tasks in the workflow of making, purifying and analysing compounds. And in screening, AstraZeneca's collaboration on acoustic mass spectrometry, where a mist of sample is ultrasonically ejected from a microplate well directly into a mass spectrometer, has demonstrated a significant reduction in assay development time and expense[6]. At a speed of three samples/second, the use of acoustic-MS in primary high-throughput screening reduces the percentage of false hits due to its label-free mass spectral data.

These and other areas of opportunity can be addressed successfully with the sort of multi-vendor collaboration described here for compound management. The kinds of sophisticated, large-scale projects that pharma and biotech companies embark on often need so many resources and specific kinds of expertise that assembling a team of outside vendors is the only viable option for delivering a robust solution.

Of course, it is also necessary to have realistic expectations about these large collaborations. Co-ordinating a project across several companies, all with individual objectives, inherently comes with a lot of risk. Mitigating this risk relies on the final products aligning with the strategic direction of all business units involved and a shared commitment among the teams. Throughout the collaborative process, all parties must continually evolve the plan and address risks. Also, a clear understanding of the total investment for such large, long-term projects is essential, as well as being able to put those numbers in the context of opportunity cost and the competitive advantages of the products. These aspects can be difficult to quantify, but they are critical factors in determining if a collaborative approach like this is worthwhile.

References

1 Ledford, H. AstraZeneca launches project to sequence 2 million genomes. Nature 532, 427-427 (2016). doi:10.1038/nature.2016.19797.

2 Wigglesworth, MJ. Murray, DC, Blackett, CJ, Kossenjans, M and Nissink, JWM. Increasing the delivery of next generation therapeutics from high throughput screening libraries. Current Opinion in Chemical Biology 26, 104-110 (2015).

3 Turmel, M et al. An innovative way to create assay ready plates for concentration response testing using acoustic technology. JALA: Journal of the Association for Laboratory Automation 15, no. 4 (2010): 297-305.

4 Griffith, D et al. Implementation and development of an automated, ultra-high-capacity, acoustic, flexible dispensing platform for assay-ready plate delivery. Journal of Laboratory Automation 17, no. 5 (2012): 348-358.

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5 Schneider, G. Automating drug discovery. Nature Reviews Drug Discovery (2017). doi:10.1038/nrd.2017.232.
6 Sinclair I, Stearns R, Pringle S, Wingfield J et al. Novel Acoustic Loading of a Mass Spectrometer: Toward Next-Generation High-Throughput MS Screening. J Lab Autom. 2016 Feb;21(1):19-26. doi: 10.1177/2211068215619124.
7 Mcgilvray, A. Compound screening: Fresh hunting ground. Nature 533, (2016).
8 Rees S, Gribbon P, Birmingham K, Janzen WP, Pairaudeau G. Towards a hit for every target. Nature Reviews Drug Discovery. 2016 Jan;15(1):1-2. doi: 10.1038/nrd.2015.19.
9 Kogej, T et al. Big pharma screening collections: more of the same or unique libraries? The AstraZeneca-Bayer Pharma AG case. Drug Discovery Today 18, 1014-1024 (2013). http://dx.doi.org/10.1016/j.drudis.2012.10.011.
10 Mullard, A. European Lead Factory opens for business. Nature Reviews Drug Discovery 12, 173-175 (2013).
11 Horvath, D et al. Design of a General-Purpose European Compound Screening Library for EU-OPENSCREEN. ChemMedChem 9, 2309-2326 (2014). doi: 10.1002/cmdc.201402126.

Pooling resources

Throughout the drug discovery and development industry, more and more organisations have come to the realisation that no individual company will be successful on its own. The need for collaborative efforts has led to an era of increased co-operation among pharma, biotech and academic research centres[7].

Compound sharing is one trend that has enhanced library diversity for a number of organisations. AstraZeneca, for instance, has teamed up with Sanofi to freely share nearly a quarter-million compounds and has an agreement with Bayer through which each pharma is able to screen new targets against both companies' entire compound portfolios[8,9]. The trend to open up pharma compound collections for screening against academic research centre targets has gathered pace in recent years. At AstraZeneca, this has created the demand to support more than 30 additional hit-finding campaigns annually with subsets of the corporate compound collection. There are many such agreements in the industry today, underscoring a willingness to combine expertise in the interest of helping all organisations accelerate the time to finding a hit for any given target.

One of the reasons these collaborations are so popular is that academic institutions are centres of fundamental biological understanding for the targets of interest in drug discovery. From generating more information about biological targets to screening compounds, projects that once consumed significant resources and risk at pharma and biotech companies are now being performed in academia, often funded by government or disease foundation grants.

Many of these academic groups and their pharma partners are sharing novel compounds to help the broader research community. The European Lead Factory is an excellent example: seven pharmas pooled and donated 270,000 compounds while smaller companies and academic teams contributed 230,000 compounds to create the Joint European Compound Library[10]. Similarly, EU-OPENSCREEN is a new project that aims to use a share-and-share-alike approach to encourage users of its compound library to contribute results from their own bioactivity research to the rest of the network[11]. Here at AstraZeneca, scientists from the Medical Research Council and Cancer Research UK will share a collaborative space in the UK Center for Lead Discovery at AstraZeneca's research centre in Cambridge, UK, accessing our compound library to test novel drug targets.

The progress being made from this spirit of collaboration will be a critical driver for developing effective new therapies. Distributing the challenges and costs of hit discovery across many more organisations – including academic research institutes – is a smart means of mitigating risk and accessing the best science.

Looking ahead

Thanks to more frequent co-operative hit discovery programmes, the need for increased screening capacity is pronounced. As we learn so much more about targets, drug discovery scientists must have access not only to more screening but also to smarter screening.

At AstraZeneca, this situation drove us to make a significant investment in rethinking our approach to compound screening – everything from where those compounds are stored to how rapidly they can be accessed and assayed. With a multi-vendor collaboration we have managed to develop and integrate new automation, labware and software to enable a completely novel approach to compound storage and management with major implications for screening capacity and speed, as well as reduced costs. While this will add real value to our own discovery pipelines, it is an approach that could be implemented by any organisation willing to make such a commitment. Innovative automation and collaboration will be integral to a future of smart screening and accelerated drug discovery. DDW

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