Collaborating with industry to find chemical hits versus difficult targets

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Background

The contraction in early stage research within Pharma has seen a renaissance in drug discovery within the academic setting. However, certain challenges for these smaller units remain. Alongside the flow of quality, novel targets for exploitation, the delivery of quality hit matter against these targets can be challenging. Whilst oncogenic kinases are considered to be druggable and hit matter can often be found from relatively modest compound collections, more complex and challenging targets, such as certain epigenetic modifiers or protein-protein interactions, require larger compound collections to deliver quality hit matter. Furthermore, determining how druggable (or otherwise) a novel target may be, and thus the requirements in terms of the size of the collection to be screened, forms an important but often overlooked aspect of target evaluation. Through novel collaborative approaches, we have sought to address these issues in an effort to deliver credible, tractable, and robust hit matter against challenging and putatively "undruggable" targets in epigenetics and DNA repair (1).

Discussion

Being embedded in a research institute funded by Cancer Research UK allows unprecedented access to a wealth of emerging biological research. As a result of this, we are fortunate to also have access to pre-publication, emerging targets. However, as these are often unprecedented in terms of target class or protein type, the druggability of the target is largely unknown. Prior examples of this would be kinases and epigenetic targets, both of which were, upon emergence, the subject of debate as to whether selective modulation was plausible. This question is only truly addressed once potent, selective and drug-like ligands have been identified and shown to display biological activity, often several years later. This de-risking exercise falls within our remit, but we do not have the resource or funding to direct our efforts toward the investigation of every such target which attracts our interest. We have, therefore, developed approaches which enable us qualitatively to assess the relative chemical risk of a target before it enters our full portfolio, and determine the most appropriate and cost-effective screening approach.

Central to this approach is the biochemical screening of a small, diverse fragment library, kindly provided to us by the Beatson Institute for Cancer Research Drug Discovery Unit (Glasgow, UK). Rather than using this library for hit finding, we use the qualitative output of the screen to derive a hit "fingerprint" which reflects the relative "ligandability" of a novel target (Fig. 1). Whilst quantitatively this approach has some potential drawbacks (such as the potential

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for false hits) we have found the qualitative output correlates well with actual druggability and HTS output (Table 1). These results mirror comparative exercises reported by AstraZeneca (2).

For druggable targets such as some kinases, a higher proportion of fragments display activity at the target and the fingerprint is enriched. For epigenetic targets, such as LSD1 (3) and SMARCA (4), the fingerprint suggests lower ligandability and, potentially, the requirement for a more extensive screening collection. For previously undocumented targets, such as the dehydrogenases and some DNA repair targets, the sparse fingerprint indicates lower relative ligandability. Whilst this does not preclude their investigation, it does suggest that a larger

**Table 1. Correlation of CRUK-MI DDU HTS campaign output and ligandability assessment**

| Target   | Predicted ligandability | Observed HTS hit rate |
|----------|-------------------------|-----------------------|
| G6PD     | Low                     | 0%                    |
| Tdp2     | Low - Moderate          | 0.25%                 |
| mtIDH-1  | Low - Moderate          | 0.7%                  |
| PARG     | Moderate                | 0.9%                  |
| LSD1     | Moderate - High         | 0.45%                 |
| RET      | High                    | 7.5% (kinase subset)  |

**Fig. 1.** Ligandability fingerprints. Bars indicate fragment hits for a specific target. Lighter bars indicate weaker hits (50–75% inhibition) and darker bars, stronger hits (75%+ inhibition). Fragments not hitting any targets are not shown.
screening collection may be required to deliver hit matter. For example, the epigenetic modifier LSD1 is known to be inhibited irreversibly by tranylcypromine-derived compounds (5, 6). However, high quality reversible modulators of this target, which displays a large, flexible and open binding pocket, are scarce (7). Our assessment suggests that such an approach should be technically feasible and work on this area is ongoing (8). In stark contrast, wtIDH has been proposed as an oncology target, when functioning in the reverse direction (9, 10). However, our ligandability assessment yielded no fingerprint whatsoever, suggesting this was an extremely difficult target to inhibit chemically.

These data permit an objective assessment of hit finding strategy: For more accessible targets, screening focused subsets or smaller HTS collections may be adequate to deliver robust hit matter. However, for more challenging targets, a more extensive collection will likely be required to deliver tractable start-points with appropriate properties. For a small enterprise such as our own, the screening of a compound collection in the order of a million compounds or more is unfeasible. To address this capability gap, we have chosen to foster novel interactions with external partners.

One opportunity which the contraction of early phase research in pharma has presented to us is the availability of high quality “off the shelf” programs which have little or no resource to aid their prosecution. Of these targets, many already have identified hit matter and may also have early SAR and/or supporting structural biology. By alleviating the requirement for hit finding, we address two common key issues around target identification/validation and identification of tractable hit matter at once. Moreover, if we are successful, we are also likely to have a potential future collaborator aligned to pick up the later stage development and clinical prosecution. Such collaborations have offered us strategic access to technologies outside our internal capabilities, allowing us to rapidly prosecute clinically valuable targets.

An alternate tactic involves direct access specifically to the compound collections of the pharma sector. Whilst many organizations now make library subsets available for blind screening, other opportunities exist for more collaborative and information-rich endeavors. We noted a considerable degree of spare screening capacity within industry and, if a mutually agreeable novel target can be identified, obvious synergies can be exploited to deliver hit matter against new targets. Here, the pharma partner undertakes an HTS and after joint triage, our access to this hit matter (and related information on selectivity, physicochemical properties and DMPK, etc.) allows the instigation of new internal projects under our direct control, to agreed milestone points. This approach has been extremely effective for us, instigating collaborative ventures on cancer-relevant targets with both AstraZeneca and GSK. Indeed, in a unique opportunity, AstraZeneca invited our own staff into its facility, offering access to its extensive compound collection and screening equipment.

Whilst these opportunities are valuable in addressing our hit finding needs and identifying a potential future partner, our ligandability risk assessments suggest that some targets present considerable chemical risk and require even larger screening capabilities. Examples of such targets are represented by G6PDH in Table 1, where biological rationale advocates that this risk is worthwhile, if an appropriate path to hit matter can be found.

For these cases, alternate strategies are required and our investigations have highlighted the resurgence of interest in DNA-encoded libraries. Our first screens employing this technology
are now in progress and we await with great interest the resultant output, in order to evaluate whether such an approach really can deliver tractable matter against targets which have failed other hit-finding approaches.

Future Directions

We have sought to address the common challenge of hit finding in an innovative and flexible manner which we believe increases both the quality and efficiency of our output. This has been delivered through innovative collaborations, pragmatism and the creative use of technologies and resource. Exploiting synergistic collaborations with industrial partners, we feel that our portfolio of hit finding collaborations allows us more readily to prosecute targets from the apparently druggable to those targets with measurable activity but with challenging or unknown druggability.

This diverse strategy offers an opportunity for us to both de-risk and prosecute novel biological targets in cancer. As a key part of this prosecution, we are also able to deliver novel, specific and drug-like chemical tools to biological partners which, in due course, will undoubtedly facilitate the unravelling of hitherto unexplored biology and ultimately deliver more robust target validation.

More importantly, we believe the approaches we have described are not specific to ourselves, but could be more widely applicable to other similar facilities. Given the present expansion of drug discovery activities in the academic, charitable, and not-for-profit sector, we hope the successful demonstration of these strategies will encourage the pursuance of additional industry-academic partnerships across diverse therapeutic areas. Whilst we believe this will result in increased efficiencies and quality of research, we trust it will also ultimately lead to the delivery of improved therapeutics to patients with cancer.

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