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Direct-to-Discovery: Extending Direct-to-Biology paradigms to accelerate drug discovery.

POSTER #018

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1 High-Throughput Chemistry

Our Direct-to-Biology (D2B) activities build upon our High-Throughput Chemistry (HTC) platform, delivering up to 5000 compounds per week from 7000 curated monomers and diverse, validated methodologies to explore both chemical space and biological activities.

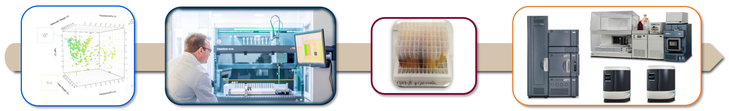

Figure 1: Our HTC workflow. Computational approaches and Generative AI influence and inform library designs, which are rapidly transformed into physical samples using robust and reproducible synthetic methods. Semi-purification, reformatting, solvent switching or full purification and QC options are all integrated into the automation platform.

2 Direct-to-Biology – Beyond Biophysics

Generally, D2B employs surface plasmon resonance (SPR) to measure kinetic off-rates for crude reaction mixtures (CRMs) as this technique is independent of conversion yields.[1] However, whilst SPR confirms target binding, it does not offer insights into functional activity.

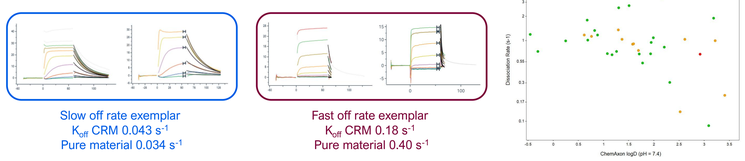

Figure 2: SPR Comparative off-rate screening of CRMs and pure materials (left, center). CRMs with ~20% product conversion and above can be identified with measurable SPR dissociation rates (right).

Through robust assay development and rigorous protocol validation, assessing reaction intermediates, reagents and solvents, we have successfully extended D2B to include functional readouts in both biochemical and cellular assays. These assays have utility in early Hit-to-Lead (H2L) campaigns, for both small molecule inhibitors and for the rapid identification of heterobifunctional degraders.

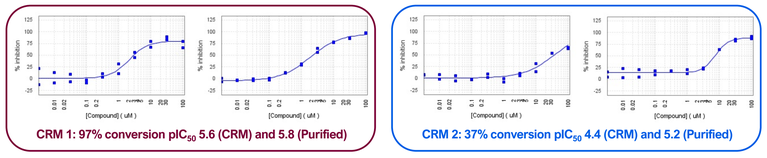

Figure 3: Biochemical screening data for CRM and purified materials for higher and lower reaction yields

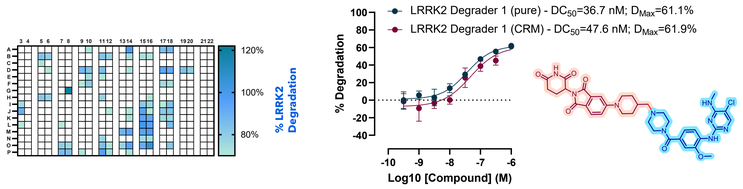

Figure 4: D2B AlphaLISA cell assay for LRKK2 degraders. Single point assays on CRMs (left) highlight robust degradation, followed by dose-response confirmation with both CRM and purified material (right).

3 Direct-to-Crystallography (D2C)

Hit validation after hit finding is critical to project success but is often rate limiting, requiring re-purchase and purification or bespoke resynthesis, adding weeks to the timeline prior to H2L entry.

Robust crystallographic systems can bypass this wait time, enriching decision making with structural data,[2] direct from 10 mM DMSO HTS screening stocks, yielding both direct confirmation of target engagement and enabling immediate entry into structure-guided optimization.

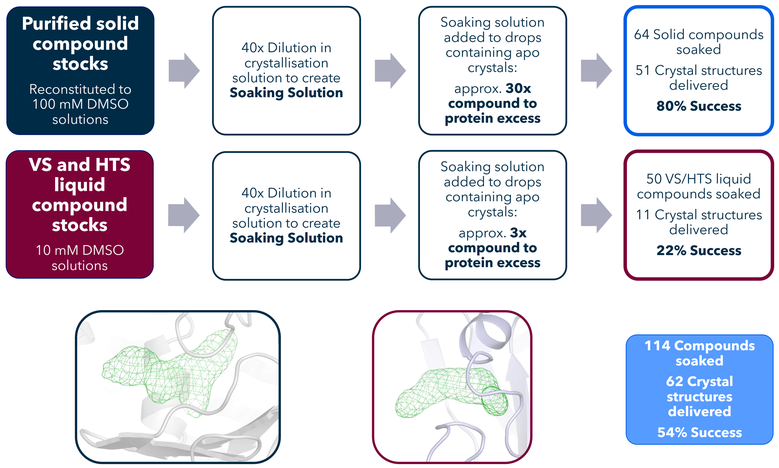

Figure 5: Direct-to-Crystal X-ray structures, with exemplar for example HTS and VS hits. (Green mesh – omit map of bound compound contoured at 3 σ).

Further acceleration of the H2L process was achieved through coupling of our Generative AI, computational chemistry and high-throughput chemistry platforms to generate focussed libraries to rapidly explore novel chemical space and opportunities to exploit novel interactions, direct from CRMs.

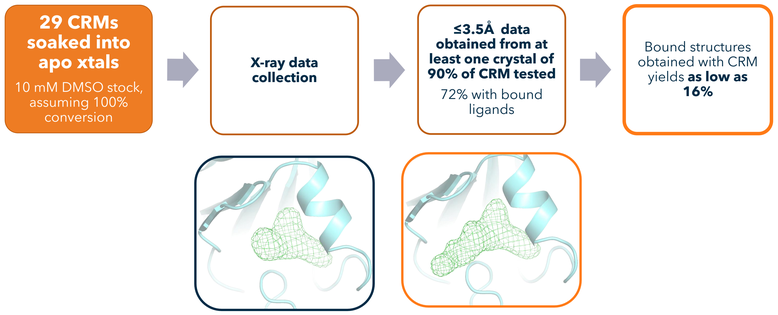

Figure 6: Omit maps of bound HTS hit and elaborated CRM derivative, prepared at 35% conversion, soaked into apo crystal, contoured at 3 σ.

4 Direct-to-Physicochemistry and DMPK (D2DMPK)

Delivering robust potency and target engagement data are essential to compound prioritisation, but an assessment of likely DMPK risk is critical to support prioritization of compounds which may become development candidates.

We have demonstrated that chromatographic methods such as ChromLogD and ePSA, which help prioritise compound selection for *in vivo* evaluation, can deliver decision-making data on CRMs, and work for both small molecules and bRo5 derivatives. This technique is concentration-independent and therefore would be anticipated to give the observed excellent correlations.

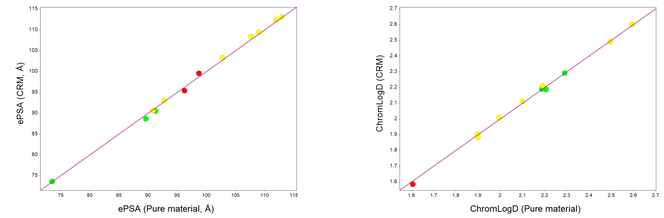

Figure 7: Determination of ePSA (left) and ChromLogD (right) for matched crude and pure samples. Colors indicate overall reaction conversion for the CRMs (0-25%, 25-75%, 75-100%).

Following work published by Merck and Co.,[3] we have also demonstrated that CRMs can be robustly evaluated in microsomal stability models, with most compounds demonstrating a good correlation between CRM and pure material. Taken together, these assays facilitate the rapid and direct prioritisation of unpurified compounds, rapidly delivered through high-throughput experimentation, into initial *in vivo* PK experiments.

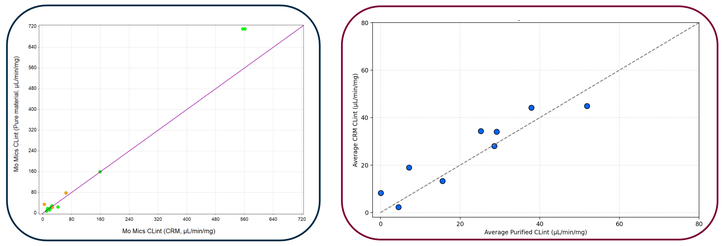

Figure 8: Determination of mouse and human microsomal stability for matched crude and pure samples.

5 Summary

Direct-to-Discovery enables the rapid generation of biochemical, cellular and biophysical target engagement data, structural insight and DMPK parameters, facilitating holistic decision-making at speed, without sacrificing quality. When integrated with High-Throughput Chemistry and Generative AI, project timelines can be significantly compressed. In the example case partly described in this poster, pre-candidate nomination occurred just 18 months, against an industry average of four years.

References 1. Baker LM, Aimon A, Murray JB, et al. Rapid optimisation of fragments and hits to lead compounds from screening of crude reaction mixtures. Commun Chem. 2020;3(1):122. | 2. Hübner AF, Weldert AC, Marciniak T, et al. Nanoscale Direct-to-Biology Optimization and Structural Insights into Selective *S. aureus* TrmD Inhibitors. J Med Chem. 2025;68(24):26246-26262. | 3. Tyagarajan S, Andrews CL, Beshore DC, et al. Rapid Affinity and Microsomal Stability Ranking of Crude Mixture Libraries of Histone Deacetylase Inhibitors. ACS Med Chem Lett. 2024;15(10):1787-1794.