Harnessing the Biophysical Fragment Screening Sweet Spot to Discover New Chemotypes for BRPF1 Inhibition

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It was estimated that the chemical universe for up to 17 heavy atoms is made of over 166 billion compounds, instead of 14.2 million for up to 11 heavy atoms.[1] This emphasises the impact an increase in the size of fragments has on coverage of the available chemical universe, and how fragment obesity can undermine the very benefits of FBDD. Although recent work has been published to address this issue, it remains a critical concern for most commercial libraries.[2]

Concomitantly with FBDD, a range biophysical screening technologies have emerged to enable the detection of weak but lean binding events associated with small molecules (typically 7-16 heavy atoms). This prompted us to push the boundaries of fragment screening by assembling a collection of small, yet diverse fragments that efficiently samples the limits of the biophysically accessible chemical universe. We believe this represents a sweet spot in fragment screening that should enable the detection of the most efficient fragment hits.

We exemplify our strategy by screening our biophysical fragment collection against Bromodomain and PHD finger-containing protein 1 (BRPF1) using the highly sensitive Grating-Coupled Interferometry technology. BRPF1 contains both epigenetic acetyl reader and scaffolding functions was recently hailed as a therapeutic target to treat acute myeloid leukaemia, medulloblastoma and hepatocellular carcinoma.[3] The range of fragments identified through our screening campaign not only validates our approach, but also provides yet unreported chemotypes enabling the development of new inhibitors for this biological target.

[1] Ruddigkeit *et. al.*, *J. Chem. Inf. Model*. **2012**, 52, 2864−2875; [2] D. Wood *et. al.*, *J. Med. Chem.* **2019**, 62, 7, 3741–3752; [3] C. L-H. Cheng *et. al. Commun. Biol*., **2021**, 4, 888.