Abstract Presentation Number: 5333

Combining chemoproteomics with machine learning identifies functional covalent fragments for hard-to-drug cancer drivers

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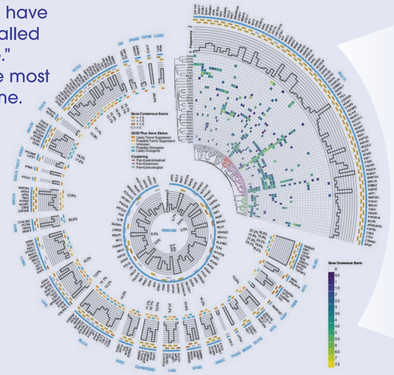
Introduction

The human genome was sequenced twenty years ago, yet current drugs target only a tenth of the proteome. Even though there are now hundreds of known cancer driver genes, we have been unable to develop tools to affect their functions, leaving patients and physicians unable to act on that knowledge.

These proteins have come to be called "undruggable." They comprise most of the proteome.



Traditional biopharma

Only **44 / 299** cancer driver genes drugged today(1)

The reason these proteins have resisted drug discovery efforts is that they lack binding sites for traditional small molecules.

Addressing undruggable targets

An improved understanding of protein dynamics, combined with innovative fragment-based approaches, has led to impressive breakthroughs against previously undruggable targets [2]. In particular, the discovery of cryptic pockets that transiently open to admit small molecules has demonstrated that proteins previously thought to be undruggable may in fact be addressable. This is especially true when applying a covalent strategy, in which a covalent bond can irreversibly capture an otherwise weak ligand, overcoming the requirement for a traditional small molecule binding site.

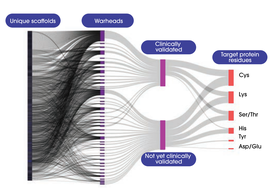
Classical screening library paradigm requiring preconfigured small molecule binding site

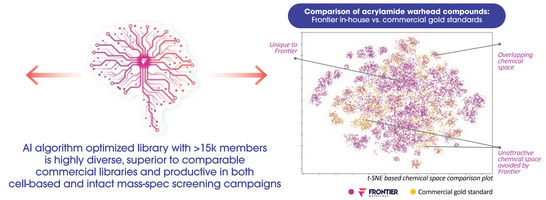
Covalent fragment screen and grow paradigm capable of discovering non-tradtional and cryptic pockets

REFERENCES: 1) Bailey et al. *Cell* 173(2018): 371 2) Erlanson, DA & Webster, KW *Current opinion in chemical biology* vol. 62 (2021):101

The Frontier™ Platform

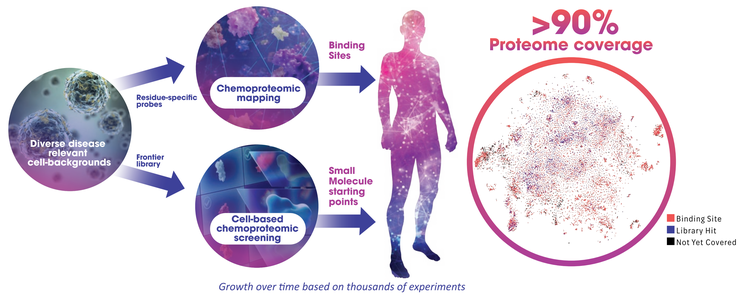
Frontier has developed a drug discovery engine combining chemoproteomics, covalent fragment-based approaches, and AI that allows us to target most of the proteome, including proteins previously thought to be undruggable. The platform consists of multiple components. Frontier's **covalent fragment library** is custom-built and continually optimized. AI algorithms have been developed to identify and guide molecules into optimal chemical property space for productive hit identification.





AI algorithm optimized library with >15k members is highly diverse, superior to comparable commercial libraries and productive in both cell-based and intact mass-spec screening campaigns

Frontier's **Druggability Atlas™** is built on a foundation of billions of experimental chemoproteomics data points. These have identified binding sites (or hotspots) for covalent modification. Additionally, a growing subset of Frontier's library has been screened against the proteome, providing immediately actionable hits.



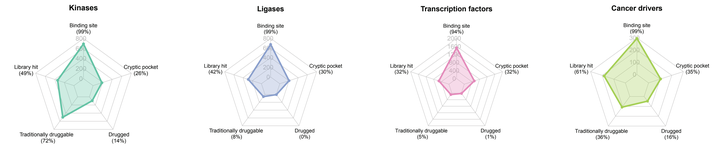
Growth over time based on thousands of experiments

Frontier combines chemoproteomics and other data with customized AI deep learning algorithms into the **Druggability Atlas™** to generate and further characterize each hotspot binding site. Chemical starting points, from the covalent fragment library profiling, as well as target validation data, are seamlessly integrated and accessible via interactive dashboards.

Activation: intrinsic reactivity of residue
Pocket: Size and ligandability of pocket
Accessibility: Access for small molecule
Target Validation: Cell line dependency
Library hit: Binding compound identified
Cryptic pocket: Cryptic pocket potential
Tissue selectivity: Proteomics/RNA based

Druggability Atlas™ covers the proteome and all target classes including previously undruggable targets

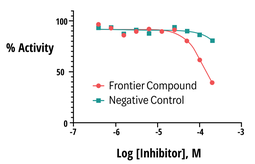
Frontier's Druggability Atlas™ shows wide coverage of profiled and well characterized covalent binding sites. Many of those sites are binding library compounds giving excellent starting points for nearly every protein target expressed in the investigated cell background. These ongoing library profiling efforts against various cancer cell line backgrounds representing multiple disease models have generated starting points for drug discovery against all major classes of targets, including hard-to-drug cancer drivers such as RAC1, HUWE1 and others.

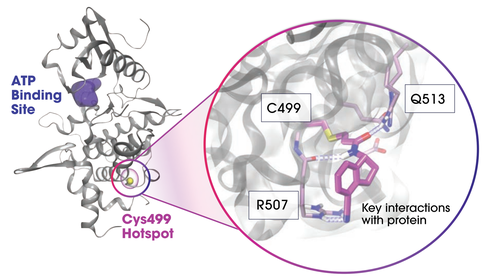


Chemoproteomics cell-based screening hits translate into functional assays

Leveraging an alternative MOA via an allosteric inhibition mechanism for druggable (or already drugged) cancer targets can potentially overcome resistances or offer an option to a differentiated patient population. Discovering those allosteric binding sites is historically incredibly difficult. The Frontier™ Platform enables the discovery of these non-traditional binding sites both at scale and proteome wide. This is demonstrated here focusing on the cancer target IRAK1, a druggable kinase target playing a role in NFKb and MAPK signaling pathways. A fragment characterized in the Druggability Atlas™ as being cell-active against IRAK1 was tested in a kinase specific phosphorylation assay and displayed respectable functional activity with an IC50 around 100uM in line with low molecular weight fragments. The fragment can be successfully modeled into the novel binding site displaying a number of important key interactions that may explain its selectivity. This represents an excellent low molecular weight starting point for an optimization campaign.

	Hits against proteome	Hits against kinome	IC50 Phosphorylation
Frontier Compound	86	5	~100 uM
Negative Control	68	5	>200 uM





Conclusions

The Frontier™ Platform has identified binding sites across >90% of the human proteome. A growing subset of identified targets also have selective small molecule ligands. The data are enriched with AI-derived insights and organized to allow rapid mining of sites and associated small molecules, without the need to run any additional experiments. Select ligands are active in cell-based and functional assays and can be used to initiate drug discovery programs, as either direct activity modulators or as starting points for targeted protein degradation. Our proprietary platform enables targeting high value cancer drivers previously thought to be undruggable and also offers alternative methods for addressing established targets to overcome resistance and increase treatment options to reach more patients.