PHOREMOST

Drugging the undruggable® For the benefit of humankind

ABOUT US

PhoreMost is a new-model drug discovery company based in Cambridge, UK, using its core expertise to open up new 'druggable' target space. Working with a global network of co-invested academic and industrial collaboration partners, we aim to bring a wide array of novel 'targeted' therapies to market more efficiently and pass these cost savings on to patients.

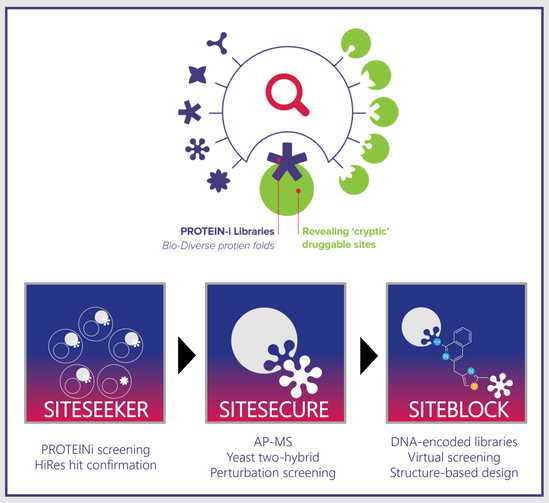
OUR TECHNOLOGY

Disease target proteins are dynamic with potential druggable pockets opening and closing and transient protein interactions in constant flux - making drug discovery difficult. New target sites need to be identified to address currently "undruggable" pathways and diseases.

PROTEINi® (Protein-interference) is a live-cell assay system that probes for cryptic druggable and protein interaction sites across all human proteins and simultaneously reveals those with a useful therapeutic function by registering a specific cellular response or "phenotype".

PROTEINi uses protein-fragment libraries based on millions of 3D-shapes to enable saturation level of target protein conformation for new druggable space and discovers hit fragments linked to a phenotypic outcome.

The SITESEEKER® platform then uses these functionally validated protein hit fragments to rapidly inform the design of small molecule drugs, providing a continuous pipeline of highly validated first-in-class drug discovery programmes for out-licensing to Pharma.

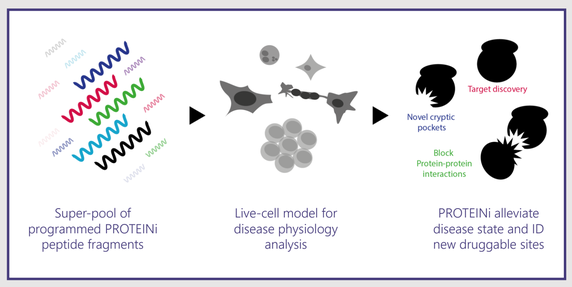


OUR STRATEGY

Advances in genomics provide a long list of clear causes of debilitating diseases and opens the door to new and improved targeted therapies. However, many of these newly characterized disease targets are intractable to current drug discovery technologies.

Using its novel SITESEEKER® technology, PhoreMost is aiming to identify cryptic druggable sites in specific disease-driving targets and pathways that can't be readily seen using conventional non-cell based analytical methods.

SITESEEKER uses live cells to probe for unexpected points of therapeutic intervention. This is achieved using diverse libraries of exogenously delivered small 3D protein-fragment shapes which interact on a genome-wide scale with host-cell proteins to describe new druggable space that is intimately linked to disease.



PROTEINi® differs from genome-based target screening technologies (such as RNAi) in that it operates directly at the protein level, so that new druggable space can be defined as an inherent part of the target-function screening process. This platform enables functional proteomics rather than functional genetic screens.

PhoreMost uses a broad range of libraries with high shape diversity which can be classified into two main groups:

- High Diversity libraries were custom built and designed for unbiased screening. These are derived from human (HuPEx), short open reading frames (smORF), bacteria (BugPEx) and across tree of life (OmePEx) proteomes. All these libraries comprise approximately 1.4 million unique sequences.
- Functionally targeted libraries are based on pathway interactomes and allow customisation for specific requirements.
  - HiRes libraries are focused to identify minimal regions involved in binding.
  - SAR libraries permit targeted mutagenesis and truncations for peptide optimization.
  - A new group of libraries, called DegraPEx, allows for PROTAC®-specific drug development.

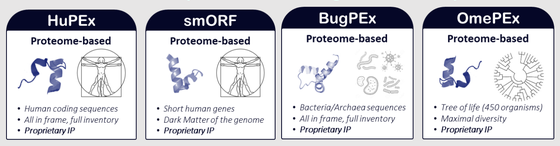
Once the library of choice is designed and manufactured, a pooled lentiviral library is generated. This library is then transduced into a screening cell line of choice and infected cells are selected.

At the endpoint of the screen, either following a phenotypic response or after a set time period, cells are pelleted, and DNA is extracted.

Using unique barcode identifiers, NGS can then be used to identify PROTEINi that have caused the desired response compared to control populations.

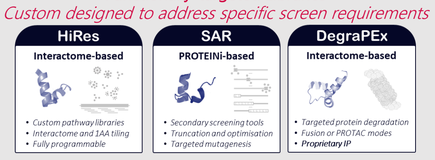
High Diversity Libraries

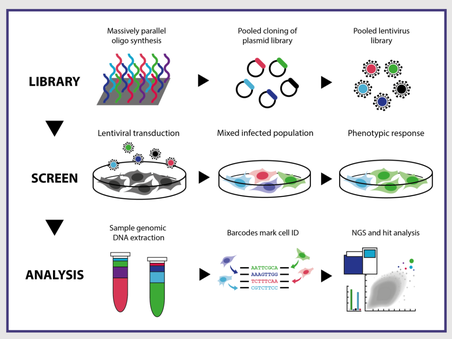
Evolutionarily enriched for biological functionality



Functionally-targeted Libraries

Custom designed to address specific screen requirements





EXAMPLE SCREEN: Ras^{G12V} Synthetic Lethality

We performed a PROTEINi® screen in a cancer cell model using the "KRAS" oncogene - a classic "undruggable" target in cancer. Ras is mutated in a large number of tumors and drives very aggressive and lethal forms of cancer. To perform this screen, we used a cell model where oncogenic Ras (KRas^{G12V}) can be turned on in cells by addition of Doxycycline (Dox). Using this model, we can now introduce our PROTEINi library using lentiviral delivery and screen for cells which die in the presence of mutant Ras after amplifying and sequencing all cells with and without induction of the oncogene after 5 days.

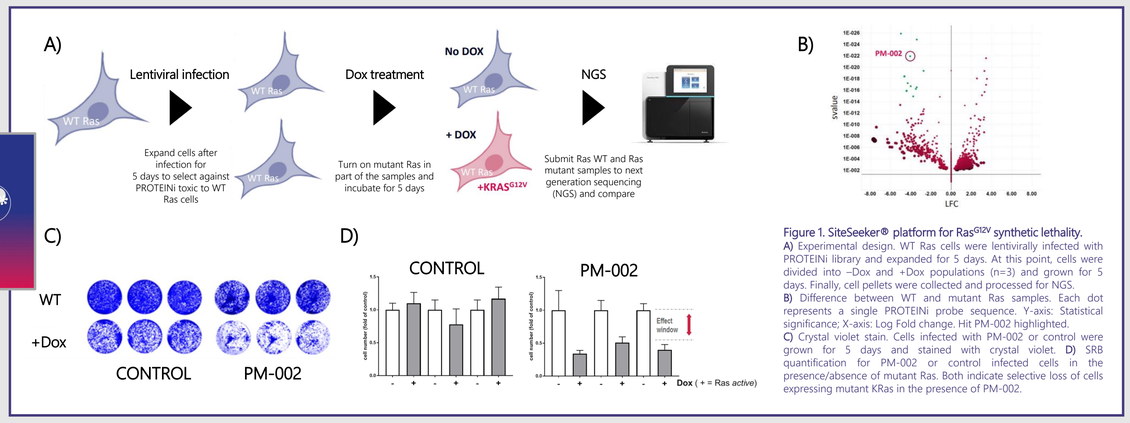


Figure 1. SiteSeeker® platform for Ras^{G12V} synthetic lethality.
A) Experimental design. WT Ras cells were lentivirally infected with PROTEINi library and expanded for 5 days. At this point, cells were divided into –Dox and +Dox populations (n=3) and grown for 5 days. Finally, cell pellets were collected and processed for NGS.
B) Difference between WT and mutant Ras samples. Each dot represents a single PROTEINi probe sequence. Y-axis: Statistical significance; X-axis: Log Fold change. Hit PM-002 highlighted.
C) Crystal violet stain. Cells infected with PM-002 or control were grown for 5 days and stained with crystal violet. **D)** SRB quantification for PM-002 or control infected cells in the presence/absence of mutant Ras. Both indicate selective loss of cells expressing mutant KRas in the presence of PM-002.

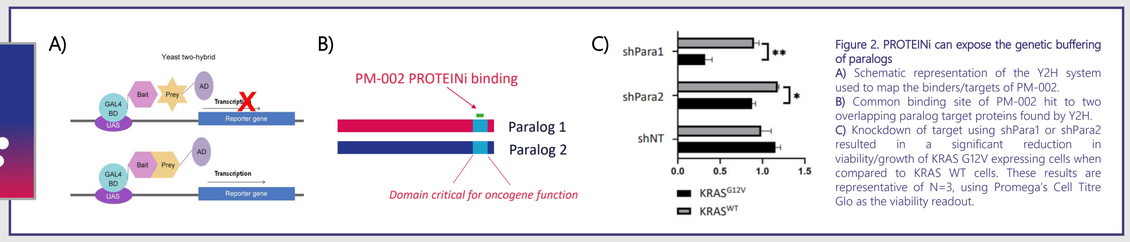


Figure 2. PROTEINi can expose the genetic buffering of paralogs
A) Schematic representation of the Y2H system used to map the binders/targets of PM-002.
B) Common binding site of PM-002 hit to two overlapping paralog target proteins found by Y2H.
C) Knockdown of target using shPara1 or shPara2 resulted in a significant reduction in viability/growth of KRAS G12V expressing cells when compared to KRAS WT cells. These results are representative of N=3, using Promega's Cell Titre Glo as the viability readout.

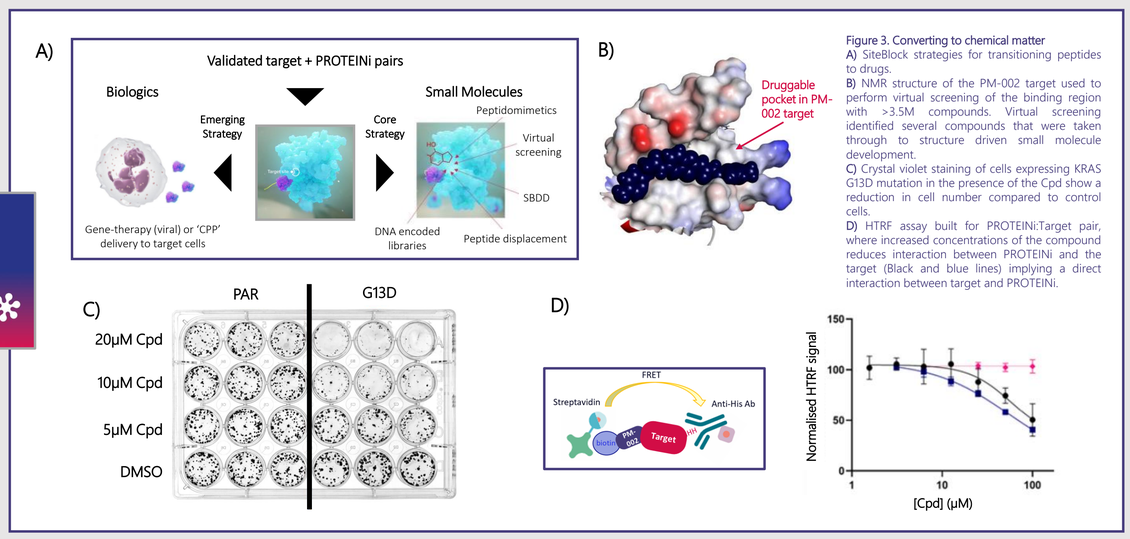
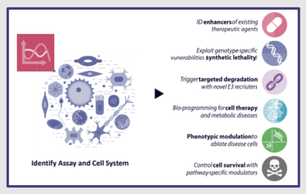


Figure 3. Converting to chemical matter
A) SiteBlock strategies for transitioning peptides to drugs.
B) NMR structure of the PM-002 target used to perform virtual screening of the binding region with >3.5M compounds. Virtual screening identified several compounds that were taken through to structure driven small molecule development.
C) Crystal violet staining of cells expressing KRAS G13D mutation in the presence of the Cpd show a reduction in cell number compared to control cells.
D) HTRF assay built for PROTEINi:Target pair, where increased concentrations of the compound reduces interaction between PROTEINi and the target (Black and blue lines) implying a direct interaction between target and PROTEINi.

Co-Development / Out-licensing to Pharma

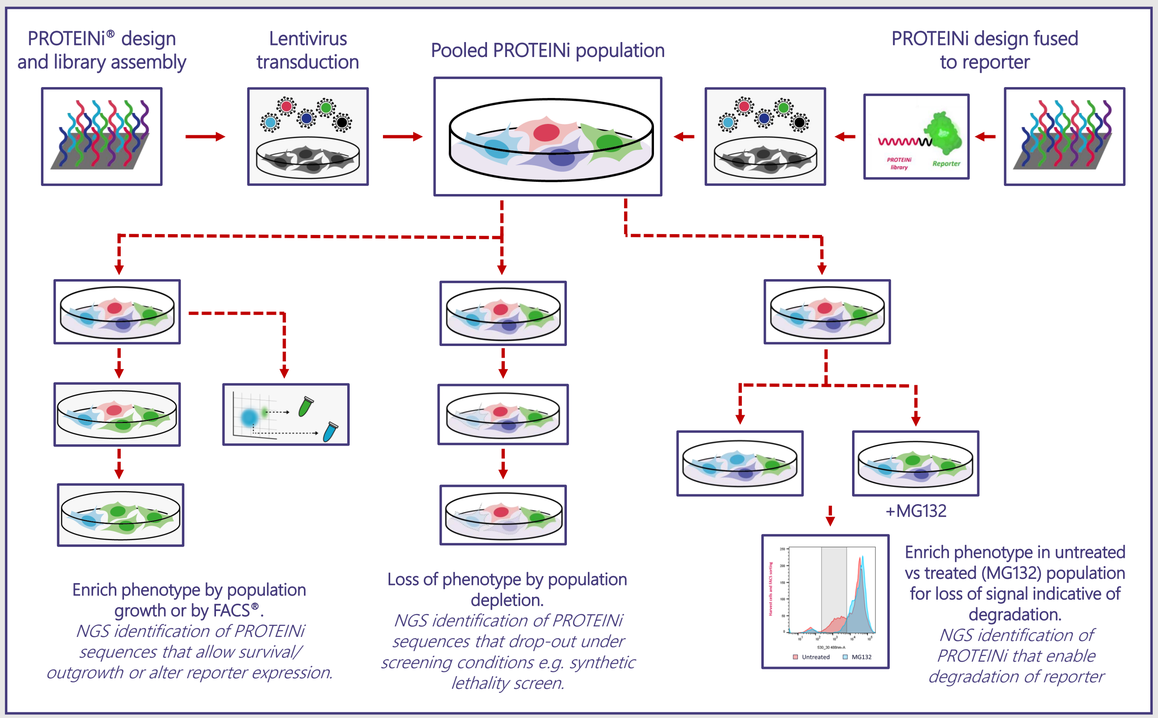
PIPELINE: Key asset development and synergistic partnerships

PhoreMost is building a pipeline of validated targets and drug discovery programs. Through the creation of new collaboration networks with industry and academia, PhoreMost is covering different areas of disease, including oncology signaling, immuno-oncology and neurodegeneration, to significantly increase the diversity of therapeutics where treatment options are currently severely limited.



Therapeutic Area	Target Validation	Chemistry Hit ID	Hit 2 Lead	Lead OP	Preclinical	PARTNERSHIPS
Oncology *Glioma, KRAS Synthetic Lethality, Inflammation*						Sentinel Oncology; XtalPi
Immuno oncology *Neoantigen creation*						
Targeted Protein Degradation *Multiple functional E3 Ligase 'linker' programs*						
External *SITESEEKER® collaborations*	Undisclosed					Novartis
	Undisclosed					Boehringer Ingelheim
	Neuroinflammation					C4XD
	Undisclosed					Otsuka
	Undisclosed					Boehringer Ingelheim
	CAR-T					OxfordBioMedica

EXAMPLES OF ASSAY CONFIGURATIONS:



OUR PARTNERSHIPS

Otsuka · OxfordBioMedica · Sentinel Oncology · XtalPi · o2h discovery · Babraham Institute · C4XD · Vernalis Research · Boehringer Ingelheim · Novartis

SUMMARY

PhoreMost uses a novel phenotypic screening method based on protein interference in the context of a collaborative drug discovery model to bring new therapies to patients more cost-effectively.

Using our peptide libraries, we have identified several new targets for drug discovery, and present work in an oncogenic Ras model as an example project here, which is currently entering the chemistry stage of our platform.

Functional PROTEINi peptides offer a rapid/rational basis for identifying druggable pockets and informing the design of novel small-molecules.

Following a collaborative drug development model, we are seeking partnerships with academia and industry to bring new drug targets out of the "undruggable" space and into the clinic.

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