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PhoreMost: Drugging the 'Undruggable'

Yi Lei Tan

Abstract: In recent years, the pharmaceutical industry has been challenged by dwindling target diversity. Some researchers conclude that reductionist approaches such as target-based screening might be limiting the 'druggable' space. PhoreMost Ltd., a new-model drug discovery company based in Cambridge, UK, is utilising a novel live-cell phenotypic assay platform to identify cryptic druggable sites in disease-driving targets and pathways. The company is aiming to bring a wide array of novel therapies more efficiently to the market by exploring new 'druggable' target space and working with a global network of academic and industrial collaboration partners.

Keywords: PhoreMost, PROTEIN i (or Protein interference), SITE SEEKER, drug discovery, live cell assay, phenotypic screening, collaboration, Cambridge

1. The success story

PhoreMost is a new model drug discovery company based at the Babraham Research Campus in Cambridge, UK. Founded in 2014, PhoreMost uses its core expertise to opens new 'druggable' targets within the human genome and bring forward novel targeted therapies more efficiently to market. The company is building on a strong heritage of excellence in developing innovative technologies and performing research on disease biology and molecular therapeutics. PhoreMost's first drug discovery program based on a novel target that addresses cancers with mutations in the gene KRAS has recently completed lead optimisation and synthetic lethal interactions of lead compounds with KRAS mutant cancer cells have been successfully demonstrated. Through establishing a global network with leading academics and industry collaboration partners, the company leverages its proprietary technology platforms to drug the 'undruggable' for a wide range of diseases.

2. How did PhoreMost start

In recent years, the attrition rate of drug candidates has been high, leading to financial loss and huge pressure on pharmaceutical companies to address the underlying factors to attrition [1].

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The identification and prioritization of drug targets in the traditional drug development process can be broadly divided into two main approaches: the bottom up approach, usually the emphasis of preclinical scientists, focuses on the biological mechanisms of disease pathology; and the top down view is typically that of clinical researchers, regulators, senior managers and customers of pharmaceutical companies, where the priority is placed on human diseases and drug targets with market opportunities [2]. An increasing gap between what can be achieved with the top down and bottom up approaches has led to a slow drying up of pharma pipelines in recent years. Whilst recent advances in genomics and basic research will allow key players in diseases to be identified, many of these newly characterised disease targets prove to be intractable using conventional non-cell based drug discovery methods. This compelled the development of a novel drug discovery platform which not only helps with identifying the best targets for eliciting the best therapeutic effects, but also provides understanding on how to drug these targets to address unmet diseases and inspires future pre clinical research on the disease mechanism.

3. The technology

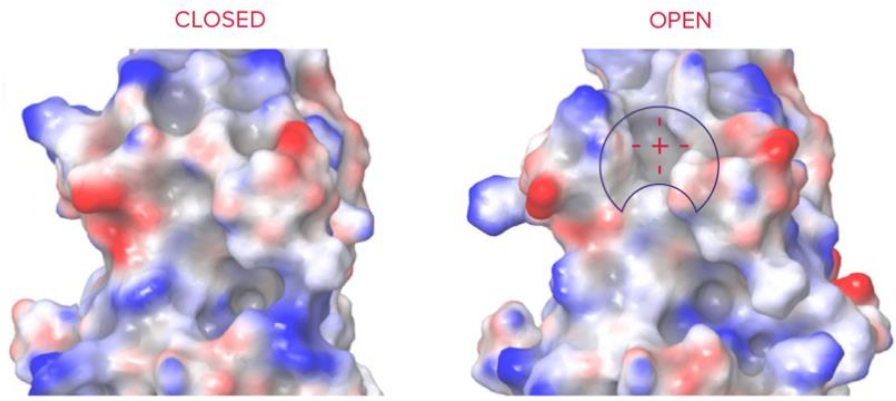

Figure 1. The inherent conformational flexibility of proteins leads to the opening and closing of cryptic crevices on protein surfaces. PhoreMost's proprietary technologies uncover hidden pockets in previously 'undruggable' targets so new druggable space can be explored.

Drug targets, composed predominantly of proteins amongst other biological macromolecules, are like cliff faces. Protein crystal structures form the foundation of traditional target based drug discovery. Chemists and structural biologists work to find key hand and foot holds on protein surfaces to design small molecule drugs that can bind to the protein and modulate its activity in biological pathways associated with diseases. Static protein crystal structures of many appealing disease targets, however, appear like sheer glass surfaces with no obvious cavities to which small molecules could bind. Yet, these static crystal structures only capture single snapshots of a protein’s structural conformations. In a cellular context, where it has proven difficult to study using conventional drug screening methods, drug targets are flexible entities with an ensemble of different conformations characterised by surface crevices undergoing opening and closing motions with distinct dynamics. These cryptic sites to which

new drugs could potentially bind, present treasure troves of new opportunities for drug development.

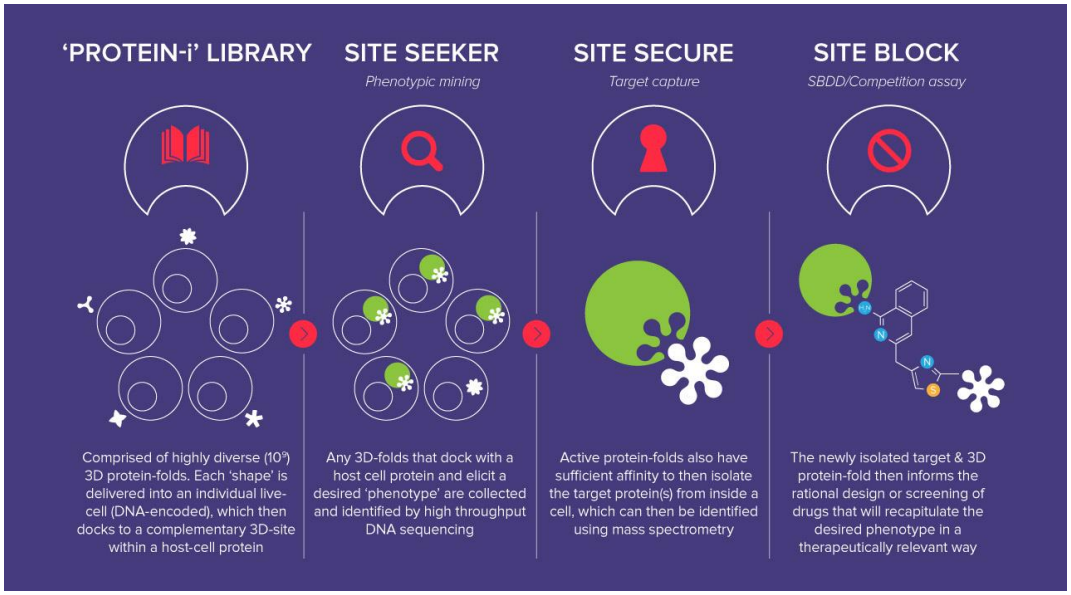

Figure 2. PhoreMost's new model drug discovery pipeline consists of four platforms: PROTEIN i®, SITE SEEKER®, SITE SECURE® and SITE BLOCK®.

PhoreMost's PROTEIN i® (Protein interference) technology is a live cell assay system that probes for hidden druggable sites across the whole human genome and simultaneously reveals those with useful therapeutic functions by registering specific cellular responses (phenotypes). A library containing up to 109 PROTEIN i probes is introduced into live cells such that each cell contains only one probe to enable subsequent unique identification of those that are therapeutically relevant. In particular, the 'Phylomer' library, which was developed by one of PhoreMost's key partners Phylogica Ltd., comprises of peptide fragments derived from different extremophilic microbes and has demonstrated high functional hit rates in mammalian phenotypic assays [3]. While technologies such as CRISPR/Cas9 and RNAi are crucial for identifying genes, which are implicated in disease pathology, PROTEIN i® operates directly at the protein level, so that new druggable space can be defined as an inherent part of the target function screening process.

Based on the proprietary PROTEIN i® technology, PhoreMost is developing a new SITE SEEKER® platform. SITE SEEKER® utilises next generation sequencing technology for high throughput scanning of DNA "bar codes" that have been attached to all PROTEIN i probes to uniquely identify selected probes which have elicited positive phenotypic responses in the PROTEIN i® live cell assay system. These probes will then be used to inform structure based design of small molecule drugs made up of the same binding motifs to recapitulate the desired therapeutic effects. Cellular targets to which the relevant PROTEIN i probes have bound can then be identified using pull down assays and mass spectrometry (SITE SECURE®). Therapeutic relevance of the designed small molecules is finally confirmed using the SITE BLOCK® platform, which involves competition assays using the small molecules to displace PROTEIN i probes from their targets and further validation using phenotypic screens. Together, the PROTEIN i®, SITE

SEEKER®, SITE SECURE® and SITE BLOCK® platforms provide a continuous pipeline for highly validated, first in class drug discovery programs.

4. The journey so far

The initial proof of concept studies on the PROTEIN i® technology were conducted in the lab of Professor Ashok Venkitaraman (MRC Cancer Unit), a lab that specialises in cancer pathogenesis and anti cancer molecular therapeutics. From the initial conception of the technique in 2007 up until 2014, the technology was gradually matured within Professor Venkitaraman's lab to achieve commercial scalability, which was marked by successful live cell phenotypic screening using up to 5,000 PROTEIN i probes. The technology captured the attention of Dr. Chris Torrance, who is a cancer researcher, entrepreneur and founder of Horizon Discovery Group plc. Dr. Torrance, Professor Venkitaraman and other founders of PhoreMost worked closely with Cambridge Enterprise, the technology transfer arm of the University of Cambridge, and PhoreMost was spun out of the university. The University of Cambridge is a foundational partner of PhoreMost, providing the core intellectual property behind the PROTEIN i® and SITE SEEKER® platforms and the company's lead program for targeting KRAS mutant cancer types. Since its founding in 2014, the company has been based in the Bioincubator at the Babraham Research Campus at the South of Cambridge. According to Dr. Grahame McKenzie, also a founder of PhoreMost, the Babraham Bioincubator has provided a supportive environment for PhoreMost and many other resident companies by providing access to exceptional technical facilities and opportunities for partnership with world class academic research labs on campus.

Since PhoreMost's early days, the versatility of the company's drug discovery model and potential application towards addressing a wide range of diseases have attracted perpetual interest from Cambridge Enterprise, venture capitals, and angel investors. By April 2015, PhoreMost has successfully raised £4m for the Series A round of funding and equity, with the equity effort spearheaded by Amadeus Capital Partners Ltd and Jonathan Milner, a founder of Abcam plc. Hermann Hauser at Amadeus Capital joined PhoreMost's Board of Directors in conjunction with the funding. Sunil Shah and Prashant Shah of O2h Ventures Ltd also made considerable contributions to the funding. In May 2015, PhoreMost was selected to receive a funding award of £1.4m from Innovate UK, the UK innovation agency, to develop its lead oncology program to target mutant KRAS cancers.

To identify the best drug targets in a wide range of diseases and to understand how to drug these targets, PhoreMost establishes close ties with academic research groups and leading pharmaceutical companies across all stages of its drug discovery pipeline. Different PROTEIN i libraries, including the Phylomer library and a library of peptide display scaffold proteins (Affimers®), were developed in collaboration with Phylogica Ltd and Avacta Group plc, respectively. These libraries lie at the heart of PhoreMost's technology platform. PhoreMost is also working with Sphere Fluidics Ltd to optimise a microfluidics platform for high throughput screening of single cells encapsulated in microdroplets, to which PhoreMost can then apply its SITE SEEKER® technology. As a key founding partner of PhoreMost, Sentinel Oncology Ltd performs precision medicinal chemistry on novel targets in PhoreMost's portfolio.

PhoreMost's current priority is to further streamline the operation of its SITE SEEKER® platform. A large portion of the Series A funding has so far been devoted towards assay development and optimisation. This reflects the inherently challenging nature of live cell assay development, as good live cell assays require faithful translation of cellular phenotypic response into machine detectable signals (e.g. fluorescence) with good signal to noise ratio and must also have the potential of scalability for high throughput screening. The company is developing different assay systems in house and in collaboration with leading experts in different disease areas, both in academia and in leading pharmaceutical companies. In March 2016, PhoreMost has established a multi project research partnership with the Wistar Institute for developing disease relevant high throughput phenotypic assays to identify and de orphan novel targets in cancer, aging and immune diseases. More recently in October 2016, PhoreMost has started collaborating with the lab of Professor David Rubinsztein (Cambridge Institute for Medical Research) to study and translate essential cellular mechanisms of neurodegenerative disorders into novel therapeutic strategies for diseases such as Parkinson's and Alzheimer's. These collaborations not only complement PhoreMost's well established oncology drug discovery pipeline but more importantly, highlight the company's scientific and corporate mantra: to find and drug the best disease targets and to engage closely with experts to tackle problems.

5. Looking to the future

At present, PhoreMost consists of a core team of 13 members with diverse expertise, ranging from assay developers to computational biologists to biochemists. By combining a strong foundation in cancer drug discovery, versatile technology platforms and a collaborative model for drug discovery, PhoreMost is looking forward to exploring novel immuno oncology therapeutics soon, with special interest in identifying the best targets and developing small molecules for "de cloaking" tumours – making them amenable to targeting by the immune system. The recent advances in gene editing and the emergence of new companies with innovative bioengineering approaches to designing therapeutics reflect the rapid progress of biotechnology innovations. PhoreMost is very confident about its ability to embrace future challenges, to be in the forefront of addressing the bottlenecks of drug discovery, and to become a world leading end to end drug discovery company that opens new therapeutic avenues in the future.

Ackgnowledgments

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The company

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Yi Lei Tan is currently pursuing a PhD in Biochemistry at the University of Cambridge. Her research has future applications in understanding membrane protein misfolding diseases, and focuses on investigating the folding mechanism of hepta-helical transmembrane proteins using biophysical techniques and NMR spectroscopy.

Yi Lei's interests lie in the life sciences and healthcare industry, especially in research commercialisation and investment. She took part in a consulting project with Cambridge Consulting Network, providing market research and financial guidance for a contract research organisation to enter the high-throughput screening market. Yi Lei joined Innovation Forum in August 2016, and has been actively involved in organising events and establishing partnerships with life science companies in Cambridge. She is currently President of the Cambridge branch of Innovation Forum, and is keen to establish strong networks amongst academia, industry, entrepreneurs and investors.