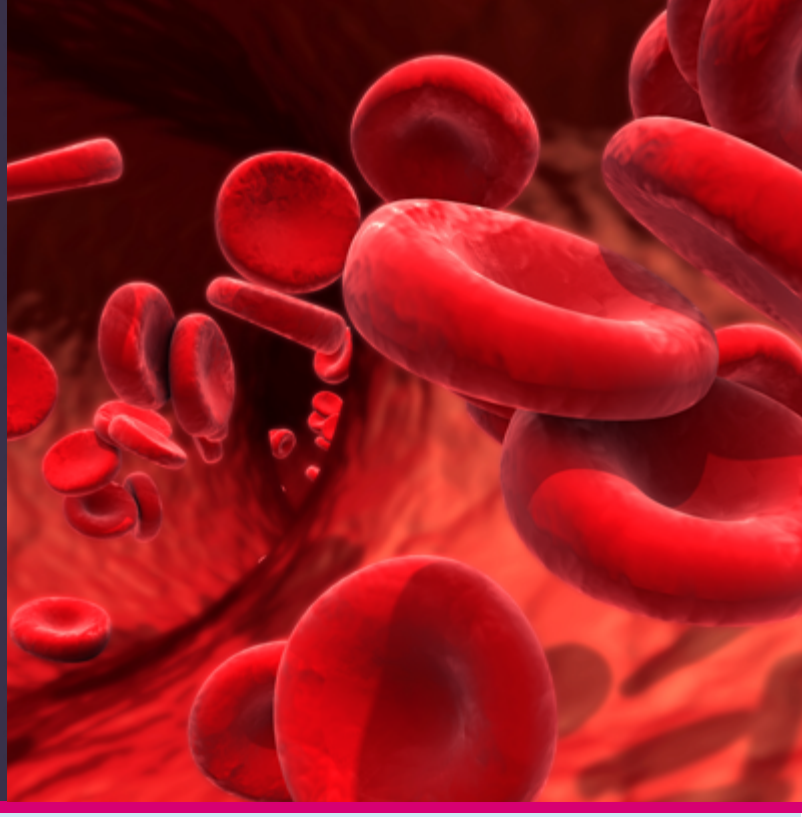
January 2023

CATAPULT
Medicines Discovery

Matters Of The Heart: Enabling Tailored Treatment for the World's Prevailing Cause of Death



PLAQUETEC

Background

Cardiovascular diseases (CVDs) are the leading cause of death worldwide – an estimated 17.9 million people died from CVDs in 2019, accounting for 32% of all global deaths (WHO.int).

The most common type of heart disease is coronary artery disease (CAD), which is responsible for the majority of CVD deaths. In this disease, a build-up of cholesterol deposits, called atherosclerotic plaques, causes the arteries to narrow or become blocked over time. This often results in reduced blood supply to the heart and could lead to ruptured or eroded plaques, leading to clot formation, which causes heart attacks and strokes.

There is no cure for CAD, but lifestyle changes, medication, and surgery are all viable treatment options.

PlaqueTec, a Cambridge-based SME, is working with researchers and clinicians to develop biomarkers (measurable indicators of the body's biological condition) to allow the accurate assessment of a patient's state of CAD and determine how likely they are to experience a future cardiac event.

This information will be used to group patients who will benefit from specific treatments and develop new treatments with higher chances of success.

PlaqueTec's novel sampling technology, the Liquid Biopsy System™, collects blood samples containing biomolecules (a type of biomarker) from upstream and downstream of the plaque's location in the artery, which can be compared to identify biomolecules leaking from plaques. These biomolecules provide information on vascular function, inflammation, and coronary plaque progression. This allows PlaqueTec to map the biological processes of CAD in more detail than has previously been possible.

A better understanding of disease status could support the development of treatments, allowing clinicians to provide more personalised treatments to decrease the number of deaths from the disease.

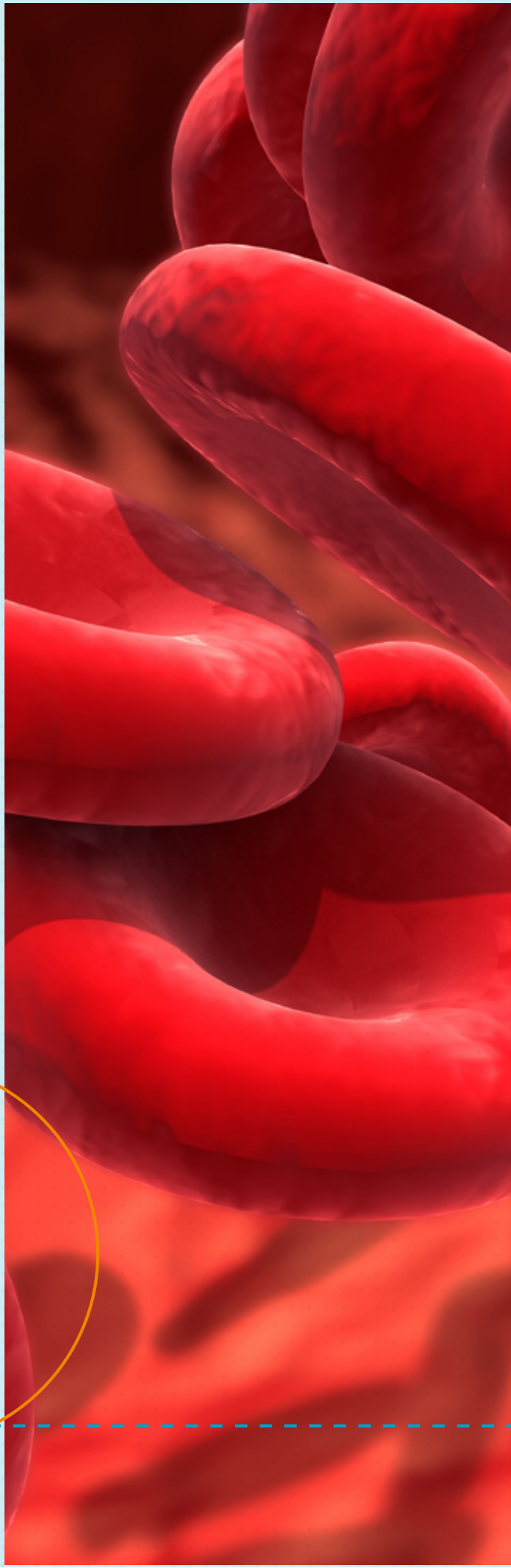
Challenge

Given that the state of disease within the coronary arteries correlates to an individual's risk of a heart attack or stroke, there is a great need for biomarkers that can reliably help clinicians predict patient risk and the extent of disease progression.

PlaqueTec has built a database of identified biomolecules to be used by CAD clinicians, researchers, and biopharmaceutical companies to conduct translational research and develop next-generation personalised therapies.

From this database, PlaqueTec generated a list of potential target proteins involved in the disease to aid the investigation of potential treatments. However, as an SME, the company needed external expertise to understand how suitable these targets might be and identify any potential compounds that would bind these targets and would be suitable start points for a drug development programme.

In February 2022, PlaqueTec was awarded an Innovate UK EDGE voucher to work on a pilot project with Medicines Discovery Catapult (MDC) to help it establish valid drug discovery targets with the potential to lead to the identification of new therapeutics for CAD.



Output

PlaqueTec provided MDC with three target proteins with varying amounts of information. MDC's experienced Informatics team ran a target assessment process on all three, bringing together over 20 different biological, chemical, and clinical resources, expert curation, and knowledge-based predictive methods to evaluate the novelty and suitability of the protein targets for small molecule drug development.

Based on several key factors; the availability of data, whether or not the target was already in clinical trials for the condition of interest, predicted druggability (whether it is possible to modify a target with a small-molecule drug), and availability of high-quality 3D structures, a recommendation was made on which target to take forward to the next stage: virtual screening.

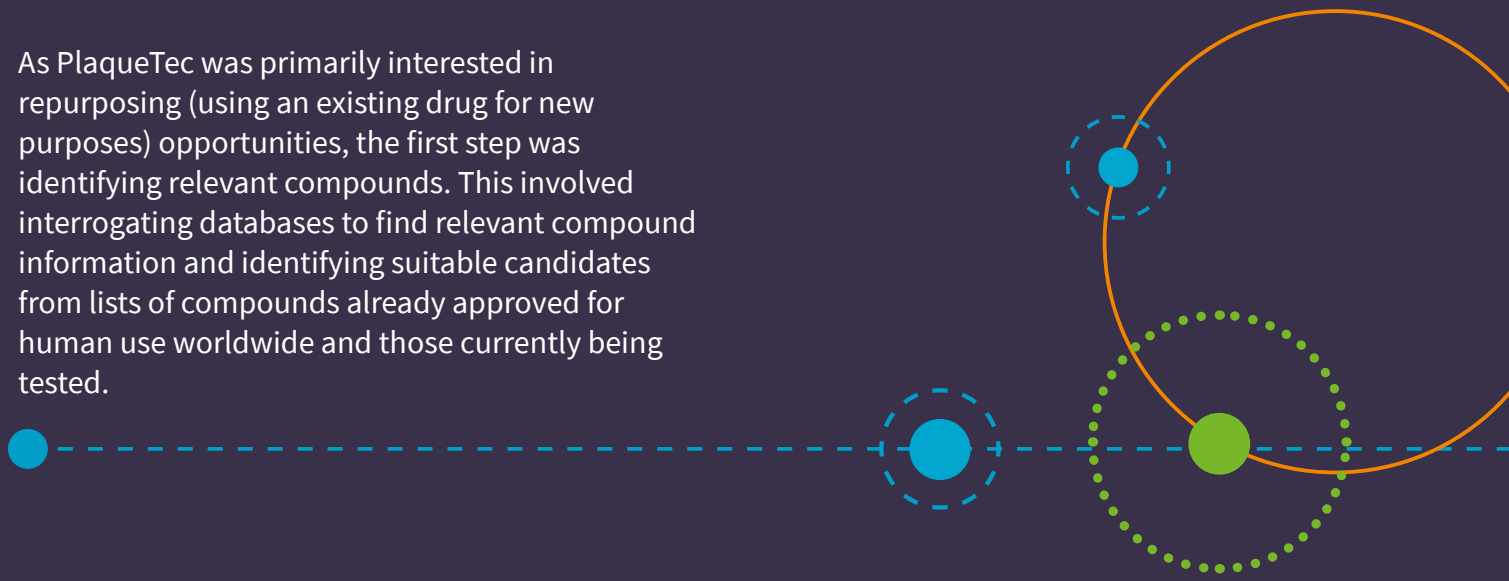
Virtual screening is a computational approach that uses various methods to determine which small molecules might be active against the protein of interest. A technique called DeepChemotyping was used for this project. It combines traditional docking methods (predicting the preferred orientation of molecules for a successful interaction) with deep machine learning to give results that are likely closer to reality. MDC's virtual screening process was used to identify potential lead compounds and further assess the druggability of the target.

As PlaqueTec was primarily interested in repurposing (using an existing drug for new purposes) opportunities, the first step was identifying relevant compounds. This involved interrogating databases to find relevant compound information and identifying suitable candidates from lists of compounds already approved for human use worldwide and those currently being tested.

Docking then takes those compounds and tries to fit them into the 3-dimensional structure of the protein of interest; molecular dynamics (analysing the physical movements of molecules) and deep learning further supplement this. Results are analysed by examining both the scores (how well the tools think they did) with a manual inspection of the interactions of the top compounds to understand the suitability of the target identified.

The outcome of the virtual screening process was a final library of compounds for consideration. These were taken into another round of assessment using many resources that hold information on compound data to gather clinically relevant data such as dosing, side effects and black box warnings (the FDA's strictest safety warnings for medicines), delivery route, and therapeutic classification.

Calculated data included models such as blood-brain barrier or cell membrane penetrability, solubility, and other physicochemical properties that may affect drug-likeness. During this process, MDC's informatics team also gathered information on clinical trials, patents, and literature occurrences to help drive novelty and suitability assessments.



Outcome

Taking such a comprehensive, end-to-end informatics approach generates significant data. As PlaqueTec is mapping the biological processes of CAD in more detail than has ever been possible, MDC knew it was essential to deliver the most relevant data tailored to the company's specific requirements. Working closely with PlaqueTec, MDC's experts provided a prioritised list of active compounds for consideration based on an enhanced understanding of the disease processes involved in CAD.

From this list, PlaqueTec has chosen three compounds for further testing. There is also scope for a larger project with MDC to conduct further studies based on the results of PlaqueTec's clinical trial.

Impact

Identifying and developing biomarkers that provide insights into tissue function and disease state at a molecular level has contributed to significant developments in several therapeutic areas. However, there has not been comparable progress in cardiovascular diseases – a gulf that PlaqueTec is working hard to close.

Using data collected from its innovative technology, PlaqueTec is developing its biomarker-based strategies to offer solutions to a disease affecting and killing a significant proportion of the global population.

MDC's unique expertise linking chemistry and biology in the informatics space meant that PlaqueTec's list of potential targets could be narrowed down to explore the biomarkers of CAD and establish if any of those proteins are interesting as drug targets for the treatment or prevention of plaque progression.

For SMEs like PlaqueTec, partnering with MDC to take an end-to-end informatics approach for target identification is infinitely more efficient and economical than conducting unnecessary wet-lab experiments, allowing greater focus.

With a refined, prioritised list of suitable compounds from MDC, PlaqueTec can now move forward on its journey to facilitate the development of new drugs that target the inflammatory processes underlying CAD progression.

MDC's expert in-house capabilities and unique approach to informatics projects are accelerating the progress of SMEs like PlaqueTec to resolve global health challenges that need urgent solutions.

Dr Diane Proudfoot, Chief Scientist at PlaqueTec, said:

"It has been a pleasure to work with MDC's cheminformatics team on this work, partly funded by an Innovate UK EDGE grant. Initially, we discussed a shortlist of potential targets identified from PlaqueTec's proof-of-concept clinical trial, which were thoroughly assessed, and one target was recommended for virtual screening.

"The result of this project is that PlaqueTec now has a detailed library of information on small molecules predicted to bind the identified target. We filtered this down to a few promising compounds to progress further and test in functional assays.

"We plan to expand this knowledge with the MDC cheminformatics team to evaluate further targets in our database and new targets generated in our upcoming clinical trial."

PlaqueTec's Chair added:

"The collaboration with MDC has paved the way for PlaqueTec to advance from biomarker discovery to fully realising its strategy of providing a full suite of diagnosis, prognosis, and precision treatment for CAD."