'Shapeshifting' computer program will open up drug discovery for tricky disease targets

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A unique computer technology that opens up the discovery of smarter drugs to treat major illnesses including heart disease has been invented by University of Strathclyde scientists.

The Shapeshifting Inspired Discovery (SID) program decodes the structures of proteins in our cells that scientists suspect may hold the key to new treatments. The program can rapidly analyse the complicated shapes and identify how the proteins might be "shapeshifted" by drugs.

Shapeshifting involves an altogether different and more subtle mechanism than conventional drugs, which stop the proteins working completely. The team behind SID – developed entirely at Strathclyde over the last decade, and now being deployed exclusively in collaboration with US firm Serometrix – will apply it to drug discovery for a wide range of diseases and conditions.

Dr Mark Dufton, of Strathclyde's Department of Pure and Applied Chemistry, said: "Conventional drug discovery is extremely expensive, time consuming and often heavily reliant on 'lottery techniques' to identify useful drugs by chance.

"While this has certainly reaped benefits before, these traditional methods are becoming less fruitful and many new drug candidates found in this way are being abandoned because of toxicity problems and side effects. Drugs that act by shapeshifting work in a much smarter way that is a closer mimic of natural mechanisms for control.

"The ability of SID to predict the scope for 'shapeshifting' enables us to probe large, complex biological molecules – which have evolved their intricate shapes over hundreds of millions of years – so that we can analyse where and whether they can be targeted to provide treatments. When targeting is more selective, and the mechanism is smarter, a new generation of better medicines beckons.

"There are thousands of different types of protein in the human system that cooperate and regulate each other so that we can function properly. Nature has evolved a beautifully intricate set of mechanisms that regulate many of our critical functions by simply changing protein shape.

"In simple terms, these 'shapeshifter' mechanisms allow the proteins to modulate their biological activity by changing their surface character, rather like tectonic plates moving around the surface of the Earth. The more we understand these mechanisms, the more we can emulate what nature has already developed so elegantly.

"Diseases are often caused by certain molecules in the body being either too active or not active enough – or by them operating in the wrong place at the wrong time. The new technology helps discovery of 'shapeshifting' drugs that can carefully adjust these biological molecules, bringing them under control and thus less likely to cause problems.

"We can use this knowledge, in the case of a specific disease, to help a key protein be more or less active when the system is not working optimally on its own."

Strathclyde Professor of Medicinal Chemistry & Drug Discovery Portal Director, Simon Mackay added: "This is an exciting step towards rapidly and efficiently designing the next wave of innovative pharmaceuticals."

Dr John Wilson, of Strathclyde's Department of Computer and

Information Sciences, said: "We've been able to understand how to optimise the SID algorithm such that it now provides a near real-time, three-dimensional, graphical output that makes it extremely easy for clients to quickly understand where to focus their efforts."

Serometrix Chief Executive Officer Mike Muehlemann said SID was already yielding promising early leads in the search for potential treatments for hypercholesterolemia – high cholesterol – and cardiovascular disease. He added: "Drug discovery and development represents one of the toughest technical challenges of our times.

"We have partnered with Strathclyde because their SID technology is best-in-class and fits exceedingly well with our own technology. The promise of better pharmaceuticals at lower cost is a lofty goal but it is one we believe we can achieve.

"With this combination of technologies we expect to reduce the number of early trial compounds from millions to hundreds, potentially shaving years off the discovery-development programme. Even though regulatory costs may remain high or escalate, an increased yield has the potential for significant cost reduction in the resulting pharmaceuticals."

Serometrix Chief Financial Officer Kyle Monroe said: "This collaboration would not have been possible without the forward thinking of Strathclyde's technology transfer office. Their ability to think and execute in an entrepreneurial fashion is one that is critical to commercial success – and could certainly provide a model for other academic institutions."

Catherine Breslin, Research & Knowledge Exchange Services at Strathclyde, said: "We are all excited about this partnership with Serometrix, as well as about demonstrating to the pharmaceutical community how a computational method combined with our drug

discovery expertise can generate new candidate medicines for a wide range of diseases."

Provided by University of Strathclyde, Glasgow