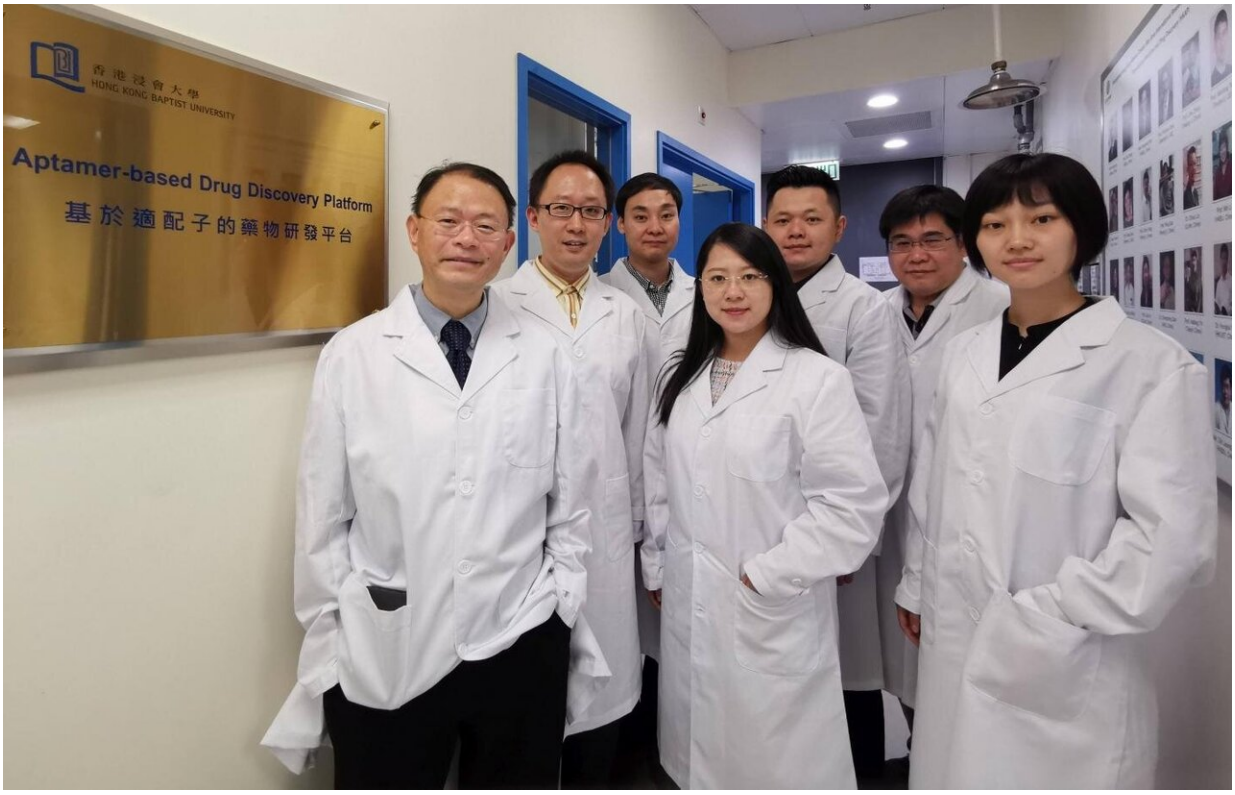
The first drug in Hong Kong to be granted orphan drug designation by the US FDA

October 23 2019



Professor Zhang Ge (1st from left), Associate Director of HKBU's Law Sau Fai Institute for Advancing Translational Medicine in Bone & Joint Diseases, and his research team members. Credit: Hong Kong Baptist University

A research team from the School of Chinese Medicine at Hong Kong Baptist University (HKBU) has successfully developed a novel aptamer,

i.e. a single-stranded piece of DNA, for the treatment of osteogenesis imperfecta (OI) with the aid of artificial intelligence (AI) technology. It is the first time a drug in Hong Kong has been granted orphan drug designation by the US Food and Drug Administration (FDA).

The designation will bring a series of benefits to the subsequent research and development of the drug, such as tax credits when conducting qualified clinical trials. The research team expects that clinical trials can be conducted in three years' time, at the earliest.

OI, which is also known as brittle bone disease, is a rare hereditary bone disease with no effective drugs for treatment. It affects 6 to 7 people per 100,000 worldwide. It is estimated that 700 to 800 people in Hong Kong have OI. Genetic studies have demonstrated that inhibition of sclerostin, a protein that regulates bone formation, can improve the clinical presentation of OI. Monoclonal antibodies, a type of biological therapy, can be used to inhibit sclerostin, but clinical evidence suggests that their use can lead to increased cardiovascular risk.

The research team—which was led by Professor Zhang Ge, Associate Director of HKBU's Law Sau Fai Institute for Advancing Translational Medicine in Bone & Joint Diseases, and Professor Lyu Aiping, Director of HKBU's Institute of Integrated Bioinformedicine and Translational Science—strategically screened and optimised a new class of molecule-nucleic acid aptamers against the sclerostin protein, which significantly promotes bone formation in mice with OI. In addition, it does not affect the cardiovascular protection function of sclerostin and hence will not increase cardiovascular risk.

Aptamers are single-stranded DNA or RNA molecules which are regarded as an alternative to antibodies. They can bind to and inhibit specific targets, such as sclerostin, with their three-dimensional structures. However, in a random single-stranded DNA library with more

than 1015 sequences, identifying the most optimal molecule for the treatment of OI is like looking for a needle in a haystack.

Aptamers can be selected, amplified and enriched through a process called Systematic Evolution of Ligands by EXponential enrichment (SELEX). Traditionally, SELEX is done manually and is very time-consuming. In this project, the HKBU team succeeded in substantially raising screening efficiency by using a microfluidic system designed by the researchers to screen the aptamers. Microfluidics is a technique which can be used to precisely control and manipulate fluid in the microlitre range (one millionth of a litre).

After screening out tens of thousands of aptamers against sclerostin using the microfluidic system, the team then applied AI technology to further identify the optimal molecules.

"We obtained thousands of candidate sequences after Next Generation Sequencing (one of the procedures of SELEX). While it is impossible to characterise the binding specificity, affinity and activity of each of these candidates, AI can calculate these characteristics," said Professor Zhang.

"AI technology saves manpower, shortens screening time, and also reduces reagent consumption. It also avoids the loss of potentially promising candidates which happens frequently when using traditional analytical methods," he added.

The novel aptamer against sclerostin developed by HKBU was granted orphan drug designation by the FDA in August 2019. In the US, the Orphan Drug Act allows the FDA to grant special status to drugs for rare disease treatment, which is referred to as orphan drug designation.

Success in obtaining orphan drug designation will bring a series of benefits to the subsequent research and development of the drug,

including the speeding up of the review process, a waiver of the marketing authorisation fee, and seven years of market exclusivity for the approved product.

"The research team is currently conducting pre-clinical research on the project. We will take receiving the FDA orphan drug designation as an opportunity to further strengthen our technological edge, and develop a more effective treatment strategy for OI in order to benefit patients and society," said Professor Lyu.

Provided by Hong Kong Baptist University