New gene therapy advance holds promise for the treatment of the global killer HBV

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The hepatitis B virus (HBV) kills between 600 000 and one million people a year globally, predominantly in sub-Saharan Africa and Asia. Life-threatening complications from HBV include liver cancer and cirrhosis.

On 25 July 2013, a significant advance in the use of a gene therapy approach to treating the virus infection was described in an article published in *Molecular Therapy*, the official journal of the American Society of Gene and Cell Therapy.

The advance is based on engineering of a new class of proteins called TALENs that can recognise and disable the DNA of the HBV. It is the result of 18 months of intensive collaborative research between the Antiviral Gene Therapy Research Unit (AGTRU) at Wits University and the Laboratory of Cell and Gene Therapy at the University Medical Centre in Freiburg, Germany.

Kristie Bloom, a PhD student who has recently completed her thesis at Wits, undertook this work as part of her degree. Bloom's research was carried out under the co-supervision of ProfessorGene Therapy Professor Patrick Arbuthnot, Kristie Bloom and Dr Abdullah Ely Patrick Arbuthnot and Dr Abdullah Ely, both from the AGTRU.

Describing the way TALENs work, Arbuthnot says: "One part of the protein specifically recognises the DNA of the HBV and another part acts as a cutting enzyme – it literally cuts the DNA of the HBV, and then

introduces mutations at the exact site of cutting, resulting in the disabling of the viral DNA."

To transport the TALENs to the HBV-infected cells, the team encodes the TALENs on engineered DNA.

"What we have demonstrated so far is proof of principle that the TALENs are effective, and that this approach could be developed as a treatment for people who are chronically infected with the HBV and prevent the risk of cancer and cirrhosis."

"However to be used as therapy, we will require vectors (carriers) that are capable of delivering the DNA to target liver cells. The focus of our current work is the engineering of viruses to serve as safe and efficient carriers of the TALEN-encoding DNA to liver cells," Arbuthnot explains.

HBV immunisation became compulsory in South Africa in 1995, which effectively prevents HBV infection. The infection is declining as a result. "However, it is of little use to individuals who are already carriers of the virus," Arbuthnot explains. "We are also confronted with a situation in sub-Saharan Africa where up until recently only 5-8% of babies had been vaccinated against HBV. The Bill and Melinda Gates Foundation is making a significant contribution to improving this cover."

What is definite is that HBV will be with us for some time to come. The prognosis for patients who develop liver cancer as a result of HBV infection is grave, and may set in anytime from the teens onwards. It is a particularly aggressive tumour and few patients survive beyond six months from the time of diagnosis of the cancer.

But the future for the treatment of HBV may be improved considerably as a result of breakthroughs like this one, which harness gene therapy

techniques.

"The term 'gene therapy' was coined in the 1970s and refers to the use of procedures that are intended to treat or alleviate disease by genetically modifying the cells of a patient," Arbuthnot explains. "The approach has enormous potential as it may be used to repair damaged genes (from, for example, inherited diseases) or silencing 'rogue' genetic elements (for example of cancers and viruses) to restore the health of cells."

The major focus area of the AGTRU is to employ gene-disabling technology to develop treatments for the persistent viral infections of serious human diseases in South Africa, such as the hepatitis B virus (HBV) and the human immunodeficiency virus type 1 (HIV-1).

"It is critical that South Africa and South African scientists participate fully in this research to avoid reliance on expertise developed elsewhere in the world; to derive maximum benefit from this powerful new technology and to maintain a strong standing in the international research community.

"The South African government has committed to developing a knowledge-based economy, which is commendable and the work we do is in line with this."

The AGTRU was launched in 2002 and the past eight years have been a busy time for the unit with the creation of new knowledge, technology, patented intellectual property (IP) and postgraduate student training, which are essential for advancing gene therapy for viral infections.

An important focus of the research unit is to provide world-class medical science training for young South African scientists. Particular emphasis is being placed on ensuring the demographics of South Africa are represented in the composition of the research team. Collaboration with

labs from all over the world is also key to create synergy from the pooling of resources.

"One gene therapy drug was licensed in Europe during late 2012 and several promising drug treatments are now in various stages of clinical testing. We would like to make rapid progress with advancing gene therapy for HBV but the timeline is difficult to predict," says Arbuthnot. Research on gene therapy has gained considerable momentum and the coming years are likely to witness exciting and significant developments in the treatment of HBV infection.

More information: www.nature.com/mt/journal/vaop …/abs/mt2013170a.html

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