

Nucleic acid therapeutic for novel therapeutic target: DNAzyme targeting c-Jun (Dz13)

DNAzymes: Business Opportunity

DNAzymes (deoxyribozymes) are single-stranded all-DNA catalytic antisense molecules that hybridize to their target RNA via Watson-Crick base-pairing and cleave at an unpaired purine/paired pyrimidine junction via their catalytic domain.

DNAzymes represent a potential new class of nucleic acid-based drug because of their capacity to perform multiple turnover cleavage, the relative ease and low cost of synthesis, and flexible rational design features.

Professor Levon Khachigian and his team at the Centre for Vascular Research at the University of New South Wales (UNSW) were the first to deliver DNAzymes into an animal model of human disease in 1999 and have defined the field of DNAzyme therapeutics.

The DNAzymes developed at UNSW are:

- stable in serum (3'-3'-linked inverted T)
- relatively easy and cheap to synthesis
- non-toxic in pre-clinical studies.

Advantages of DNAzymes over siRNA include:

- made entirely of phosphodiester linkages, not phosphorothioate groups
- cheaper to synthesise
- more stable than siRNA
- self-sufficient catalysis and do not require the recruitment of catalytic cellular machinery (such as Dicer/RISC) to degrade target substrate.

Lead Target and Lead Product: c-Jun DNAzyme (Dz13)

The lead product is Dz13, a DNAzyme targeting the 'master regulator' transcription factor c-Jun.

c-Jun represents a novel target for inhibition of intimal thickening, neovascularisation, tumour angiogenesis and inflammation, as it works upstream of and regulates transcription of many pathogenic mediator, including: VEGF and FGF.

Dz13 inhibits inducible c-Jun protein expression and DNA-binding activity in

microvascular endothelial cells. Dz13 blocks endothelial proliferation, migration, invasion and microtubule formation *in vitro*.

Lead Indication:

Basal cell carcinoma (BCC) is the most common malignant skin cancer.

BCC incidence varies depending on geographic region. Australia has the highest rate of BCC in the world and its incidence are increasing at a rate of 5% annually.

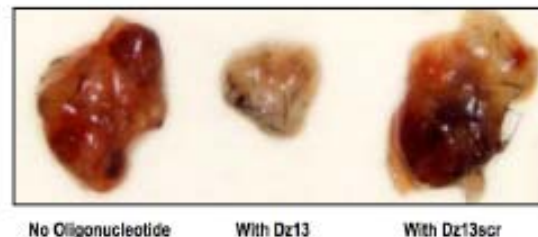
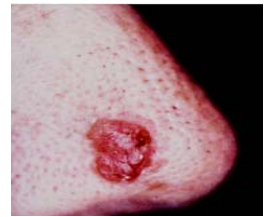
There is an acute need for alternative strategies to treat BCC.

Currently, the main treatments for BCC include:

- surgical excision
- imiquimod (Aldara) for superficial BCC (30% of cases).

Dz13 has the potential to treat nodular BCC (70% of cases), thereby avoiding tissue scarring and disfigurement. Supporting evidence includes:

- Dz13 inhibits B16 melanoma growth and tumour angiogenesis in C57/B16 Mice
- Dz13 inhibits UV-induced squamous cell carcinoma (SCC) growth and tumour angiogenesis in SCID mice
- Dz13 inhibits c-Jun expression in solid SCC tumours
- Dz13 inhibits MMP-9, VEGF-A, MMP-2 and FGF-2 expression in solid SCC tumours.



Dz13 but not scrambled sequence (Dz13scr) inhibits solid B16 melanoma growth in mice.

Single Product, Multiple Therapeutic Applications:

In vivo animal studies are underway to explore clinical use of Dz13 in the following indications with large unmet needs:

- rheumatoid arthritis (RA)
- age-related macular degeneration (AMD) and diabetic retinopathy (DR)
- restenosis, in-stent restenosis and bypass graft stenosis
- heart damage after heart attack (myocardial infarction).

Supporting evidence from in vivo animal models demonstrate that Dz13 inhibits:

- retinal neovascularisation
- vascular permeability
- cytokine induced inflammation
- IL-1 inducible inflammatory gene expression
- neutrophil infiltration in the lungs of LPS-challenged mice
- synovial neutrophil infiltration and neovascularisation in arthritic mice
- joint inflammation and bone erosion.

Local versus Systemic Delivery

The BCC, RA, AMD and restenosis are diseases amenable to local drug administration, reducing the possibility of unwanted side effects and maximising drug concentrations in the desired tissue. Professor Khachigian, however, is also engaged in collaborative efforts to achieve systemic DNAzyme delivery using state-of-the-art lipid-based approaches.

Funding

Funding of \$2.96 million over 5 years has been secured for this program via a Cancer Institute NSW Translational Program Grant, covering preclinical and early clinical studies.

Scientific Team

Professor Levon Khachigian and his team at the Centre for Vascular Research at UNSW have an exceptional track record in research and commercialisation, with over 130 publications, (including in Science, Nature Biotechnology, Nature Protocols, J Natl Cancer Inst and Nature Medicine) and numerous patents.

Patent Position

The base patent 'Vascular Therapeutics' is in national phase in AU, CA, EU, JP, US [PCT/AU03/00237 filed 27/02/03 (WO/2003/072114), patent term expiry 2023]

A method of preventing or reducing angiogenesis and/or neovascularization by administering a nucleic acid which decreases the level of c-Jun mRNA, c-Jun mRNA translation or nuclear accumulation or activity of c-Jun; a method for inhibiting onset of restenosis by administering nucleic acid molecule; dependent claims to DNAzymes, ribozymes, antisense oligonucleotides, ssDNA targeted against c-Jun dsDNA; angioplastic stent comprising c-Jun inhibitory nucleic acid molecule (PCT claims).

'Treatment of Rheumatoid Arthritis' is in PCT phase [PCT/AU2007/000914, patent term expiry 2027].

A method for treating or inhibiting rheumatoid arthritis in a subject by administering a nucleic acid which decreases the level of c-Jun mRNA, c-Jun mRNA translation or nuclear accumulation or activity of a c-Jun protein; dependent claims cover DNAzymes, siRNA, antisense oligonucleotides, ribozymes, ssDNA targeted against c-Jun dsDNA, dsRNA targeted against c-Jun mRNA.

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