ANNEXURE A

CURRICULUM VITAE

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QUALIFICATIONS
BSc, University of the Witwatersrand, 1981
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OVERVIEW OF CURRENT RESEARCH AND FUTURE PLANS

Applying gene therapy to advance new treatments of viral infections of South African Importance

Background
The elucidation of the structure of DNA in 1953 provided important insights into the make-up of genes. This led logically to an improved understanding of gene function and investigating the therapeutic possibilities of modifying gene function. Since genes are central to all biological processes, controlled alteration of gene function has enormous potential application as a mode of therapy. 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. The approach may involve the repairing of damaged genes, as is the case for treatment of inherited diseases, or silencing 'rogue' genetic elements that are produced in cancers or during viral infections. Since gene therapy potentially has such broad utility, the approach is rapidly becoming part of mainstream research of modern molecular biology and medicine. Although hurdles remain, the possibilities are exciting, and it is likely that new solutions to overcoming serious diseases will emerge from harnessing gene therapy techniques. Recent discovery of the powerful and specific RNA interference (RNAi) gene silencing pathway has given further impetus to the therapeutic possibilities of gene modification. Development of engineered nucleases (TALENs and Zinc Finger

nucleases) that are capable of digesting and disabling DNA at specific sites has also been an exciting advance that has powerful therapeutic potential. The research focus of my work is to utilise new methods of gene silencing to counter hepatitis B virus (HBV) and HIV infections, which are of particular public health importance in South Africa.

Therapeutic silencing of HBV and HIV replication.

Hepatitis B virus (HBV) was one of the first viruses to be linked causally to a human tumour. Together with tobacco, it is now thought to be the most important environmental carcinogen to which humans are exposed. There are approximately 387 million carriers of HBV in the world today and as many as one-quarter of these will develop hepatocellular carcinoma (HCC). HBV is implicated in the aetiology of as much as 80% of the HCC that occurs with such high frequency in sub-Saharan African and Asian populations. Individuals who are chronic carriers have a greater than 100-fold increased relative risk for developing the tumour. Licensed treatments for HBV infection, which include IFN-α, nucleoside and nucleotide analogues, are limited by side effects, cost and variable efficacy. Although there is an efficient vaccine to prevent infection, vaccination is ineffective against established infections and problems related to persistent HBV infection are likely to continue for many years. Advancing new modes of treating persistent HBV infection is therefore an important medical objective, and use of RNAi-mediated specific gene silencing techniques has shown promise. Research carried out by the applicant has involved a series of investigations that have been aimed at optimising anti-HBV RNAi activators (see recent publications). Initially, a panel of antiviral sequences was assessed and the most powerful silencers were selected for further analysis. Derivatives of these sequences were incorporated into cassettes that can prevent the emergence of viral escape and also limit unintended side effects. This has been achieved by improving dose regulation and generation of multiple antiviral elements. Our research has shown that chemically synthesised nanoparticles and engineered adenoviral carriers are capable of delivering antiviral sequences and achieving potent silencing of HBV replication in vivo in a stringent mouse model of HBV replication. Principles derived from understanding the HBV gene silencing mechanisms were applied to HIV-1 subtype C and efficient knockdown of this important viral strain was demonstrated. A new field of work in our laboratory is the advancement of TALENs and Zinc Finger Nucleases that can be employed to cleave the cccDNA of HBV. This topic is particularly exciting as eliminating cccDNA has been the major impediment to advancing HBV therapy.

Ongoing research

A major hurdle that has hindered widespread use of gene therapy is the inadequate efficiency and safety of delivery of gene-modifying sequences. Engineered viruses and chemically synthesised non viral vectors have been used with variable success. Concerns about safety have been an impediment to use of viral vectors, while poor delivery efficiency limit the utility of chemically synthesised non viral vectors. The focus of the proposed research is to develop the use of new generation engineered adenoviruses to deliver anti HBV sequences to the liver. Adenoviruses have the important advantage of delivering genes to the liver with high specificity, but a drawback is their strong and potentially toxic stimulation of an immune response. To overcome these problems, research will be aimed at the use of helper-dependent or gutless adenoviruses as well as capsid-derived virus-like particles. Importantly, HD Ads have all of the adenovirus genes removed. The infectious particle is constituted through the transient action of a helper virus, which is removed during purification of the gutless adenoviruses. The vectors are sterile, and incapable of propagating themselves in the absence of a helper virus which makes them safe to use. Chemical modification of HD Ads and virus like particles will be employed to attenuate immunostimulatory effects and also confer tissue targeting properties. In addition to RNAi activators, we are developing the use of HBV sequence specific

TALENs and Zinc Finger nucleases. These engineered nucleases have the particularly important property of taregting HBV cccDNA to cause sequence disruption that results from double strand breaks and non-homologous end joining. Successfully disabling cccDNA function in a clinical setting will be a major advance for HBV therapy. Research in our laboratory is carried out in collaboration with research partners in South Africa, Europe, the USA and Asia. The desired outcome of our research will be the development of innovative solutions to a serious viral infection of public health importance to South Africa. Investigating this topic also provides a useful means of instruction for postgraduate research students.

RESEARCH COLLABORATIONS

1 Dr Nicolas Ferry, Laboratoire de Thérapie Génique, Centre Hospitalier Universitaire de Nantes, France.
2 Joachim Engels, Institut für Organische Chemie und Chemische Biologie, Johann-Wolfgang-Goethe-Universität, Frankfurt, Germany.
3 Claudio Mussolino & Toni Cathomen, Laboratory of Cell and Gene Therapy, Center for Chronic Immunodeficiency, University Medical Center Freiburg, Freiburg, Germany.
4 Professor Philip Ng, Baylor College of Medicine, Houston, Texas, USA.
5 Professor Mario Ariatti and Dr Moganavelli Singh, University of Kwa Zulu Natal, Durban
6 Piet Herdewijn, Laboratory of Medicinal Chemistry, Rega Institute for Medical Research, Katholieke Universiteit Leuven, Belgium.
7 Professor Michael Kew, Department of Medicine, University of Cape Town, South Africa.
8 Professor Charles de Koning, School of Chemistry, University of the Witwatersrand, South Africa.
9 Professor Willem van Otterlo, University of Stellenbosch, South Africa.

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