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JAMES GEAR FELLOWSHIP: 1993-4

STUDY TOUR FROM DECEMBER 92 TO JAN 94 WORKING IN LABORATORIES AT ST MARY'S HOSP MEDICAL SCHOOL, LONDON AND INSERM. PARIS

While preparing to submit my PhD thesis in 1992 my PhD supervisor, Prof Wyn Fitschen, recommended that I gain broader experience by working in an overseas laboratory. The late Professor Michael Kew, with whom we were collaborating at the time, suggested that I approach Christian Bréchot to enquire about opportunities in his laboratory at Necker Hospital in Paris. Prof Bréchot had a successful INSERM research laboratory that focused mainly on hepatitis B virus, which was also the topic of my PhD thesis. I was pleased that he accepted my request to join his team, and the opportunity could be realised with support of the James Gear Fellowship.

My thesis was submitted towards the end of 1992 and I started working at Necker Hospital in January 1993. Christian was keen that I should be part of a newly formed team within the laboratory which was exploring use of gene therapy to treat HBV infection and complicating liver cancer. The subject was new to me and seemed interesting. I worked closely with

Nicolas Ferry, the leader of the gene therapy team, and we engineered retroviral and adenoviral vectors (carriers of genetic material) that could deliver potentially therapeutic genes to liver cells. The results showed good efficacy in cultured cells, but the vectors were unfortunately not efficient in vivo. These observations were similar to the findings of others working in the field. Nevertheless, the research was published in good journals and I remained enthusiastic about the potential of gene therapy to treat various diseases, not only HBV infection.

I was in Paris in 1994, which was also the time of transition to democracy in South Africa. Together with many South Africans living in France, I voted in the first democratic elections at the South African embassy in Paris. Buoyed by these positive developments, I decided to return to SA and establish a laboratory that worked on using gene therapy to treat viral infections, particularly HBV. At the end of 1994, I rejoined the Department of Medical Biochemistry at the University of the Witwatersrand. The laboratory's beginnings were humble, but support was forthcoming and the team grew steadily. Over the subsequent 29 years, good funding was attracted, new staff joined and many students were trained on gene therapy. Two of these students, Marc Weinberg and Sheena Saayman, were themselves recipients of James Gear Fellowships. The laboratory subsequently received unit status at the University, and was named the Antiviral Gene Therapy Research Unit (AGTRU). The Unit became an extramural unit of the South African Medical Research Council in 2014, which was another significant milestone.

The focus of research continued to be on developing gene therapy-based treatment for infection with HBV, but work was also carried out on other viruses such as HIV, HCV and Rift Valley Fever Virus. Technology that was developed included production of therapeutic mRNA, gene silencers, gene editors and engineered recombinant viral vectors. Emergence of the COVID pandemic had a significant impact on research in the AGTRU. During 2020 and 2021, it was clear that health security of low- and middle-income countries (LMICs) was compromised because of limited access to vaccines. Moderna and Pfizer/BioNTech showed that mRNA vaccines were effective against SARS coronavirus-2, which heralded a new era of vaccine technology. Significance of the development was recognised by the WHO, which lobbied first world countries for aid to establish an mRNA vaccine platform in LMICs. Experience of AGTRU with using mRNA to treat HBV infection was strategically important to advance the technology in LMICs. AGTRU thus became involved in providing technical support for teams from South Africa and LMICs to advance use of mRNA in vaccines. After proving efficacy of a SARS-CoV-2 vaccine that encoded the viral spike protein, other

candidate vaccines have been developed. Employing the technology to advance new methods to prevent infection with Mycobacterium tuberculosis and HIV, amongst others, is in progress. Abdullah Ely and Kristie Bloom, two PhD graduates from AGTRU, are driving this promising work. As well as using mRNA, AGTRU has engineered recombinant adenoviral vectors that can be used as vaccines. Experience with adenoviruses, originally gained while in Paris, has recently been advanced by Betty Maepa from AGTRU, has been used to provide technical support to Biovac, the leading vaccine manufacturer in South Africa.

Overall, receiving the James Gear Fellowship had a significant influence on shaping my career. Particularly important was the opportunity to enter the field of gene therapy and more lately to harness the technical know-how from this experience to assist with development of new nucleic acid-based vaccines.