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Department:
Science and Technology
REPUBLIC OF SOUTH AFRICA



The story of the three strands: MMV390048

H3-D is born

The idea of a drug discovery centre in South Africa was first raised in a discussion between Professor Kelly Chibale and an ex-colleague, Dr Frederik Deroose in Beerse, Belgium in June 2007. Frederik had considerable experience in managing drug discovery in his role at Jansen and Jansen, and mentioned to Kelly that this would be a good thing for Africa to contemplate.

About the same time, the University of Cape Town was actively promoting the concept of "signature themes", which formed part of an institutional policy framework for the establishment of inter-disciplinary research themes that stimulate high-level collaborative research. This process led to the selection of drug discovery as a signature theme at UCT, formally linking research groups in the faculties of science, health sciences, and engineering to create a new dynamism and collective collaborative mind-set.

The South African Department of Science and Technology (DST) was experimenting with a new concept of awarding key scientists research chairs under the South African Research Chairs Initiative (SARChI). This initiative was administered through the National Research Foundation (NRF) in a number of disciplines in academia in South Africa. Following competitive rounds, Prof Kelly Chibale was nominated by UCT and was subsequently awarded the DST/NRF SARChI Chair in Drug Discovery from 1 January 2008.

The remit of the appointment was to concentrate on the discovery and pre-clinical development of novel medicines or treatment modalities for the major communicable diseases in South Africa, while training a new generation of South African scientists with the key modern pharmaceutical industry skills required to discover modern medicines.

Seeking to be better equipped to deliver on the outputs of the sort required by the DST/NRF SARChI Chair, Prof Chibale spent a sabbatical (September-December 2008) as a visiting professor at Pfizer, Sandwich, in the UK. During this sabbatical Prof Chibale was exposed to integrated modern drug discovery and recognised the essential skill and infrastructure components that would be the pillars of H3-D.

Collaboration with MMV

In early 2008 in Geneva, Switzerland, Dr Tim Wells, Chief Scientific Officer at the Medicines for Malaria Venture (MMV), was about to embark on an ambitious plan to conduct a high-throughput screening campaign. This campaign would test several millions of chemical samples to identify new compounds active against the blood stage form of human malaria caused by the parasite *Plasmodium falciparum*. The campaign was to be conducted in collaboration with

Professor Vicky Avery at the Eskitis Institute at Griffiths University in Brisbane, Australia. Subsequently the DST, in 2010, funded Prof Kelly Chibale to visit the Eskitis Institute to study their drug discovery capabilities.

In Cambridge in the UK, UCT alumnus Dr Richard Gordon, then the European Director of Business Development at BioFocus, was seeking to set up drug discovery collaboration with MMV, on the basis of MMV screening the proprietary compound collection of BioFocus. A deal was agreed in June 2008, although there was much discussion on who would implement the programme once screening was complete. Richard and Tim discussed the possibility of conducting this in South Africa, and Richard made contact with Kelly in June 2008

As a follow-up to the contact between Richard and Kelly, the pivotal meeting was held on 17 July 2008 between Kelly, Richard, Tim and Richard Davis of the Wellcome Trust, at Terminal 1 of Heathrow Airport in London, to discuss how this could be accomplished. They drew up a draft business plan for a drug discovery centre at UCT using the MMV project as an anchor programmed to build skills and resources.

This business plan was first presented and discussed with Glaudina Loots, the Director: Health Innovation at the DST, on 18 September 2008. Glaudina recommended that this should be pursued with the DST through Cape Biotech Trust (CBT). With supporting letters from MMV and Pfizer, Kelly approached CBT with a proposal to provide funding towards establishment of infrastructure to implement the MMV programme.

CBT (now part of the Technology Innovation Agency) approved the proposal and an initial agreement was formalised in late 2009 to complete the set-up of the platform. In the same year, CBT and UCT Research Contract and Intellectual Property Services provided seed funding to develop a detailed business plan for the establishment of a sustainable drug discovery centre.

In April 2010, H3-D was officially born.

The MMV390048 project: true international collaboration

The H3-D-MMV project commenced on the 1st April 2009 with a small team of chemists taking forward the BioFocus compound series, identified from screening at Eskitis by Prof Vicky Avery. The in vitro and in vivo biology was carried out at the Swiss Tropical and Public Health Institute (Swiss TPH) and in vitro/vivo pharmacokinetics at Centre for Drug Candidate Optimisation at Monash University – Australia. MMV appointed an experienced project mentor Dr Michael J Witty, who had 30 years of pharmaceutical industry experience with Pfizer. In addition, UCT outsourced some contract chemistry to Syngene – an Indian contract research organisation.

The project has been run as a true international collaboration with real-time sharing of data, monthly project meetings and real scientific excellence being leveraged from around the globe, including tapping into the MMV network of large pharmaceutical companies such as GlaxoSmithKline and Novartis. The project has been highly successful in generating capacity in South Africa. H3-D has built significant expertise in the area of in vitro pharmacology and medicinal chemistry, with the UCT team growing from four to 10 members. In addition, the programme has been very influential in helping to leverage additional resources in the form of facility upgrades, clinical expertise and finances.

In 2010, a DST Health Initiative – the South African Malaria Initiative (SAMI) – agreed to fund the transfer of technology from the Swiss TPH to UCT, to conduct all the in vitro parasitology using sensitive and resistant strains in South Africa. This had a significant, positive impact on the project timelines and deliverables while increasing the skills of the South African team.

To date the chemistry team on the project has made more than 500 samples, tested in disease models – the first example of such a programme of its kind in Africa. Patents were filed, protecting the intellectual property, and a paper published in the Journal of Medicinal Chemistry this year describes some of the drug discovery that led to the identification of the breakthrough compound.

In September 2010, a compound code named MMV390048, which subsequently displayed exceptional potency against the parasite, was first designed and made. The compound is stable, and showed significant promise in an in vitro experiment. It was tested in animals in early 2011. The resultant data was even more encouraging as MMV390048 displayed a complete cure of animals infected with malaria parasites when given orally (by mouth) at a low (20 mg/kg) dose. More importantly, the drug remained in the animal for a long time – preventing any potential regrowth of the parasite.

This result is outstanding in view of the fact that clinically used drugs such as the artemisinins, chloroquine, and mefloquine do not achieve a single oral dose cure in the same animal model. Artesunate and chloroquine both require four daily oral doses of 100 mg/kg, while mefloquine requires, four daily oral doses of 30 mg/kg to achieve a cure in the same animal model in which MMV390048 was tested. The promise of the compound was further demonstrated when tested against a number of drug-resistant strains from Africa and Asia: MMV390048 was lethal in all strains.

During the second half of 2011 and in early 2012, extensive testing of the compound has been carried out to fully characterise the molecule and its close relatives with respect to efficacy and safety. This data was compiled and submitted to the MMV Expert Scientific Advisory Committee. This highly respected panel consists of a number of very experienced pharmaceutical members who have a long history in drug discovery and clinical development. The compound was unanimously approved for clinical development in July 2012.

In January 2012 MMV and TIA agreed to build on the success of the programme and signed a four-year collaborative deal to deliver back-up chemical series and to develop additional chemical compounds to take forward. This is a truly groundbreaking collaboration.

Background on Professor Kelly Chibale

Professor Kelly Chibale joined the University of Cape Town in 1996 as a lecturer and rose through the academic ranks to become full Professor of Organic Chemistry from 2007. His research is in the field of drug discovery.

Kelly is a full member of the UCT Institute of Infectious Disease & Molecular Medicine (IIDMM). In 2008 he was awarded a Tier 1 South Africa Research Chair in Drug Discovery under the South Africa Research Chairs Initiative (SARChI) of the Department of Science and Technology (DST) and administered through the National Research Foundation (NRF). In 2009 he became the founding Director of the Medical Research Council (MRC) Drug Discovery and Development

Research Unit at UCT. In the same year (2009) he was elected a Life Fellow of UCT and a Fellow of the Royal Society of South Africa. In 2010 he became the founding Director of the UCT Drug Discovery and Development Centre (H3-D).

Kelly obtained his PhD in Synthetic Organic Chemistry from the University of Cambridge in the UK with Stuart Warren (1989-1992). This was followed by postdoctoral stints at the University of Liverpool in the UK as a British Ramsay Research Fellow with Nick Greeves (1992-94) and at the Scripps Research Institute in the USA as a Wellcome Trust International Prize Research Fellow with KC Nicolaou (1994-96). He was a Sandler Sabbatical Fellow at the University of California San Francisco in the USA (2002), a US Fulbright Senior Research Scholar at the University of Pennsylvania School of Medicine in the USA (2008) and a Visiting Professor at Pfizer in the UK (2008).

Background on Dr Richard Gordon

Dr Richard Gordon grew up in the Eastern Cape, where he completed matric at Selborne College. He studied a BSC at UCT and completed his PhD in 2000. He moved to the UK where he completed a post doctoral stint at the University of Cambridge in the group of Professor Andrew Holmes.

In 2002, Richard left academia and joined BioFocus, a small contract research organisation in Cambridge UK, as a senior scientist where he worked as a scientist on drug discovery programmes. In late 2003 he tasted success as the lead chemist on a research programme that delivered a clinical candidate for rheumatoid arthritis. At the same time, he was offered an opportunity to develop his business development skills and, in 2004, was seconded into the European Business Development team responsible for the UK and Scandinavia.

Five years and three mergers later, Richard was appointed global head of Business Development and Marketing for BioFocus - a position that consolidated BioFocus as one of the most successful pre-clinical contract research organisations in the world. During this time Richard set up more than 50 major research programmes with pharmaceutical companies, biotech companies and major not-for-profit organisations in the US, EU and Asia Pacific. He is also a chartered marketer.

Richard's yearning to return home was facilitated through two important programs. In 2009, in his capacity at BioFocus, he initiated the successful MMV/UCT partnership in partnership with Kelly Chibale and Tim Wells. In 2010, in his capacity at BioFocus, Richard helped set up the South African TB Research Innovation Initiative (SATRII) in partnership with the NIAID – now the largest research collaboration in Africa involving five South African Research organisations.

Richard was recruited by the Technology Innovation Agency and MMV in July 2011, when he and his family returned to South Africa. Richard has considerable experience setting up and managing major collaborations and he currently plays several key roles in the South African drug discovery space.

Background on Dr Timothy Wells

Dr Timothy Wells is the Chief Scientific Officer of Medicines for Malaria Venture (MMV), based in Geneva. MMV collaborates on a portfolio of over 50 projects spanning from early stage discovery to products which are already transforming health.

During the last five years, MMV and its partners have launched four new products. These include a pediatric dispersible therapy (Coartem[®] Dispersible, with Novartis) where over 100 million treatments have been delivered, and the first prequalified injectable artesunate (Artesun, with Guilin) of which treatments for over 1 million children with life-threatening severe malaria have been supplied. MMV and its partners registered two other artemisinin combination therapies Eurartesim[®] (with Sigma-Tau) in 2011, and Pyramax[®] (with Shin Poong) in 2012.

Under Tim's leadership the discovery team at MMV has flourished, and there is now a robust pipeline of new molecules, with eight new molecules in early development, including two which have been shown to be active in phase II human clinical subjects.

Prior to joining MMV, Tim had over 20 years experience in drug discovery and development, as the head of Research for the Swiss biotech Serono, and prior to that with Glaxo. He has almost 200 publications, and recently edited a book on neglected disease drug discovery for the Royal Society of Chemistry. He has a PhD in Chemistry from Imperial College, London, UK and an ScD in Biology from Cambridge, UK. He was appointed fellow of the Royal Society of Chemistry in 2011, and Fellow of the Academy of Medical Sciences of the UK in 2012.

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