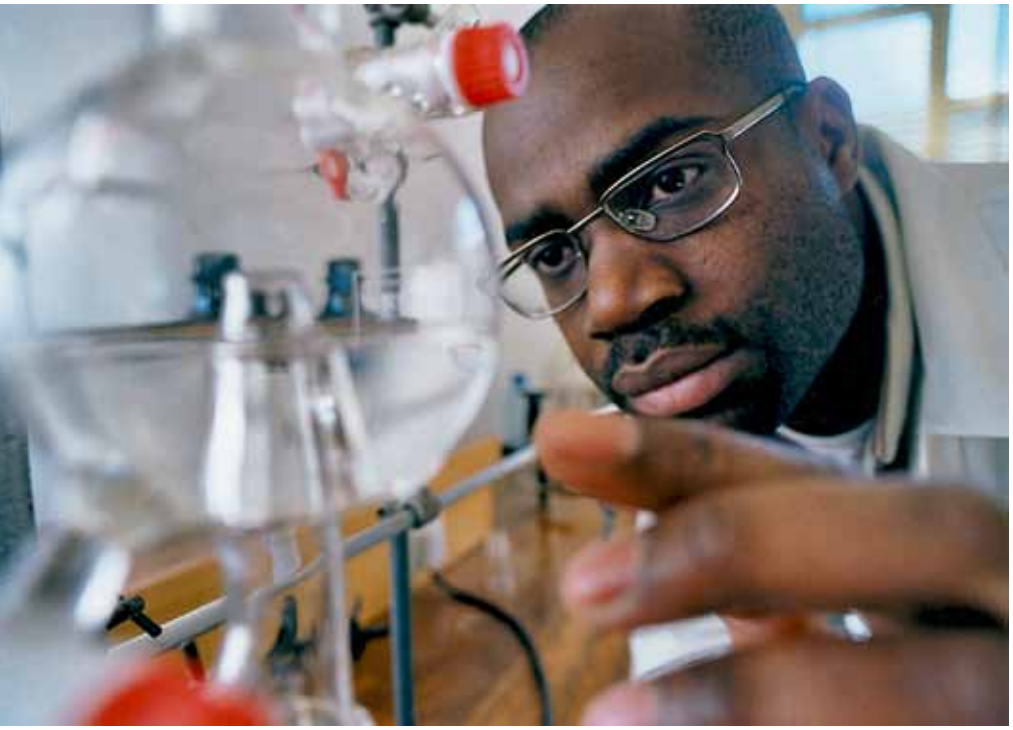
Chibale's Crusade Launches Africa's First Integrated Drug Discovery Centre



Professor Kelly Chibale's crusade to challenge Afro-pessimism and to kick-start Africa's drug discovery industry is gaining momentum as he prepares to formally launch Africa's first integrated Drug Discovery Centre at UCT in 2011.

Chibale is passionate about developing future generations of world-class scientists and creating an infrastructure and environment that will spur on drug discovery and related industries. In turn it is his hope that many more solutions will be found to counter some of the world's most devastating diseases which make their presence felt so overwhelmingly and painfully on the African continent.

While these issues are close to Chibale's heart, they also lie at the core of UCT's Drug Discovery Signature Theme – one of several research themes the University is committed to nurturing and supporting in the foreseeable future.

A Professor of Organic Chemistry with joint appointments in the Department of Chemistry in the Science Faculty and the Health Sciences Faculty's Institute of Infectious Disease and Molecular Medicine (IIDMM), Chibale has already made significant progress towards establishing the new Centre.
The vision is to create a fully-fledged drug discovery centre, whose activities mirror those of a start-up biotechnology or pharmaceutical company. The model envisaged for the Centre is that once medicinal chemistry starting points (hits) are identified within a particular project, they will then be progressed along the value chain in terms of hit-to-lead and lead optimisation. This process will utilise and integrate medicinal chemistry, biology, pharmacology, as well as drug metabolism and pharmacokinetic studies.

"Projects will tap into the expertise the Centre will offer, that being the available platforms along the value chain, as well as pharmaceutical industry know-how and associated expertise," he says.

An attendant vision is to deliver clinical candidates ready for testing in humans which will complement and strengthen the IIDMM's activities, bridging the current gap that exists between basic science and the clinical studies of various diseases at UCT.

In talking about his work the phrase "Kill quick, kill cheap," is one he often uses. It is in reference to the need to cut one's losses early on in the drug discovery innovation process if the signs of progress are in anyway tenuous. It also conveys Chibale's sense of urgency about finding potential new drugs to fight malaria, tuberculosis, HIV/AIDS, cancer, hypertension and cardiovascular disease.

"Sadly most patents in South Africa, which are filed and maintained at great cost, are meaningless in that they have little value and are not really attractive to potential partners from the pharmaceutical industry. There needs to be substantial real value added to a potential medicine before filing or maintaining a patent."

"Even when a provisional patent is filed, it's crucial to have follow-up action to access the platforms and skills required to move the molecules along the value chain as quickly as possible, and to only consider progressing the Provisional

Patent to PCT and National Filing once a true lead molecule with substantial value has been identified," he says.

Chibale believes the Centre will add substantial value to projects because potential gaps and weaknesses have already been identified. "We have put in place the necessary platforms and will be looking to bring in relevant pharmaceutical industry expertise as well as partnerships with pharmaceutical companies and 'virtual' Drug Research and Development organisations such as Medicines for Malaria Venture, Global Alliance for Tuberculosis Drug Development, BioVentures for Global Health, to name but a few."

The energetic Chibale also holds the DST/NRF South Africa National Research Chair in Drug Discovery under the South African Research Chairs Initiative (SARChI) and is Director of the South African Medical Research Council (MRC/UCT) Drug Discovery and Development Research Unit. In 2005 his laboratory was selected as one of the World Health Organisation's (WHO) Synthetic/Medicinal Chemistry "Workstations" or Centre of Excellence by its Tropical Diseases Research. At the time his lab was the only one in Africa to be singled out for this honour and has been among only a select few scattered across the globe.

Although he is immersed in the myriad tasks and minutia of detail involved in establishing an interdisciplinary Centre, he also is equally passionate about his role as a teacher and supervisor. He currently supervises some 35 postgraduate and postdoctoral students and delights in helping his students appreciate the thrill and excitement that is part of the reward for rigorous scientific research and innovation.

Chibale is candid about his initial foray into innovation, believing that he squandered valuable research time and energy, without tangible outcomes. "When I began my career at UCT in 1996 I was innocently embarking upon Drug Discovery, but in terms of really doing drug discovery as it should be done, it took me at least up until about 2007 to begin making real headway. I just was naïve and didn't know what it took to really say, 'This is a real lead'. Secondly, there wasn't an infrastructure to tap into, to make progress possible."

He points to the fact that Africa has not got a track record or history of discovering and developing modern pharmaceuticals i.e. from discovery all the way to market.

Kelly Chibale - Antimalarial Drug Discovery in Perspective

The burgeoning burden of disease on the one hand, and an annual US$350 billion market for leading therapeutic drugs, is driving the pursuit of new methods in drug synthesis, and drug development and drug target identification.

The need for safe, effective medicines must take into account the fierce competition in the drug-development industry which is experiencing considerable cost pressures.

While the traditional drug-discovery approach is to identify a therapeutic target, link this to a specific biological mechanism, and thereby provide a focus for a discovery effort, the advent of high-throughput screening (HTS) methods enable a large number of compounds to be screened in a relatively short time. These recent advances in synthetic chemistry methodology have facilitated the rapid construction of lead analogs. These lead compounds can then be subjected to a variety of substrate binding and toxicological tests to determine their efficacy as drugs.

The speed with which drug discovery is now moving can be illustrated by a project headed by Professor Kelly Chibale, in conjunction with experts in the pharmaceutical industry from across the world, which has led to the identification of novel chemotypes that are unrelated to existing drugs on the market.

Chibale is immensely proud of the project's progress thus far and candidly remarks that he feels he has achieved more in six months than he achieved in a decade of adopting the traditional approach to drug discovery.

"We started this project last year with Medicines for Malaria Venture (MMV), a 'virtual' drug research and development organization which on average spends in the order of US$60 million dollars per year just on malaria," says Chibale.

When it was formed a decade ago, MMV was the first public-private partnership of its kind. It now has the largest ever portfolio of projects on discovering antimalaria drugs in the history of mankind, and is involved in the whole process from drug discovery and development, through to clinical testing, product launching and marketing.

The MMV project involves processing hits from a phenotypic whole cell High Throughput Screening (HTS) of a commercial library purchased from the biopharmaceutical company BioFocus in the UK.

"In investigating a molecule with application for the treatment of malaria, we accessed a collection of 35,000 small molecules from BioFocus. As we don't have the capability in Africa for high throughput screening (HTS) – it's a very unique, specialised technology that is extremely expensive – we sent this library to

"There is also a critical shortage of skills in medicinal chemistry, that integrates drug metabolism and pharmacokinetic studies, which are crucial to drug discovery.

This serious shortage of requisite drug discovery skills is indeed our Achilles Heel in our quest to discover and develop our own medicines. These skills will initially need to be urgently imported onto our continent from the western pharmaceutical industry," he states.

"Although South Africa has a strong reputation in basic science and clinical studies of diseases, there has always been the challenge of how to translate this into new potential medicines. Similarly, although UCT is a leader in the area of drug discovery in Africa and also has an excellent track record in basic research, what we are really missing is being able to bridge this gap between the basic sciences and the clinical sciences," says Chibale.

"The challenge has always been how to translate what comes out of the basic research into tangible outcomes to which real value has been added," By that I mean, if you look at the whole drug discovery development and preclinical phase of development in terms of the value chain, what is seriously lacking in South Africa will actually render any of these efforts useless if we don't bridge this gap and actually put in place key platforms and technologies along this value chain that allow things to move meaningfully forward."

The establishment of the centre will be the first step in bridging that gap, creating an appropriate infrastructure for collaborative drug discovery and development and sowing the seeds for a viable pharmaceutical industry in South Africa. The centre's links with a strong global scientific network will also ensure that projects meet internationally recognised standards.

Chibale believes this combination will produce a critical mass of new scientists to develop drugs to fight infectious and other diseases, but with a unique focus on the issues facing sub-Saharan Africa.

"There's a lot of Afro-pessimism in this country and elsewhere, but I think the work of this Centre should convince any doubting Thomases that we can do excellent innovation here. Innovation is really what sustains a venture of this nature. I want the work of the Centre to be based on intellectual property and

Australia to the Eskitis Institute at Griffiths University in Brisbane for HTS," Chibale continues.

"They were able to screen this library of 35,000 molecules on malaria. Once we had established the molecule's cytotoxicity, which measures its general toxic effect on cells, and determines its safety, we then went through a process called a "Hit Triage".

"A "hit", in simple terms, is basically just something that gives you a positive result in a primary screen. So in our case, we looked for molecules in that 35,000-strong library which had an effect on parasites, and anything that gave us a positive result was simply a "hit"."

Chibale observes that even with this obvious progress, there is no point in filing a patent until further investigation is completed. Here, he pauses to talk about the role of the team that is carrying out the work and the need for it to be interdisciplinary.

"A good Project Team actually includes not just the obvious disciplines that you need to move things forward, not just chemists who make molecules, but experts in biology, genetics, drug metabolism, patenting and so on. You basically harness their combined expertise to design a molecule that overcomes any obstacles to becoming a drug. It's really a market experiment," he maintains.

As part of the triage process, Chibale and his team revisited the progression criteria in order to see if those criteria had been met. "We selected those molecules that fulfilled our criteria. The next phase was to carry out what we call "Hit Validation" – retesting, to double check that what we found was really true. After this came a very important and expensive process, the Hit-to-Lead process."

"The way that I define it, a "Hit" is simply something that gives you a positive result, while a "Lead" gives you confidence that you may have found a suitable candidate. There again, you have predetermined criteria of what characteristics a lead should have," he says.

Within the lead there are two categories: an "Early Lead" and a "Late Lead". An early lead shows that apart from its efficacy, the molecule is going to be bio-available – which involves predicting what the human body is likely going to do to the drug.

"Once the work on the "Early Lead" is completed, work begins on a "Late Lead", where you embark on "Lead Optimisation". So when you find the lead, you synthesise it and test it with respect to criteria that you defined upfront. You then make sure that you understand its liabilities and problems, which you can then address during lead optimization," Chibale explains.

He believes the lead optimisation stage is where the real innovation lies – the penultimate step before the chemist hands over to clinicians during the "Candidate Selection" phase.

Chibale takes up the story: "The HTS was conducted against malaria parasite strains at the Eskitis Institute. The goal of this MMV project is to conduct a medicinal chemistry programme on selected hit compounds from the HTS to identify quality leads suitable for optimisation and, ultimately, candidate selection as potential agents to treat various forms and stages of malaria."

Chibale explains that MMV's Expert Scientific Advisory Committee (ESAC), of which he is a member, has been instrumental to the project's progress along the innovation chain. "Before you do anything with regard to innovation you've really got to establish that there's freedom to operate, because when it comes to innovation, you really don't want to go blindly into something," he cautions.

The MMV's ESAC comprises international experts in drug discovery who have given Chibale invaluable advice, leading his team in an exciting new direction. He is grateful for the experience gained from sitting on the committee and interacting with these luminaries of the pharmaceutical industry.

"A number of the members have 30 years of experience and a proven track record of discovering, developing and putting new drugs on the market – thereby

innovation where substantial value has been added so that when you file a patent, it really is good value."

Chibale is excited about the Centre's operational model. It addition to the establishment of a drug metabolism and pharmacokinetics platform, an associated Foundation will be established to help fund various initiatives whether at UCT or elsewhere in Africa.

The Cape Biotech Trust, which is now part of the Technology Innovation Agency (TIA), has already provided funds to establish a drug metabolism and pharmacokinetics platform, which is currently housed in Chibale's IIDMM laboratories. The funds have been spent on key capital items of equipment and some staff salaries. In conjunction with MMV, Cape Biotech Trust has also contributed funds towards the secondment of two UCT postdocs at BioFocus, a British biopharmaceutical company for training in drug metabolism and pharmacokinetic studies focusing on assays.

"We are currently setting up the various assays that will be required to conduct these studies. So effectively the platform has now been established and should be in a position to provide a service to the scientific community by mid-2011. In the meantime, I am currently in discussion with TIA to provide additional funds to recruit key personnel with the relevant experience, and to keep the platform running for at least the initial few years before it becomes financially self-sustaining."

"We wanted to develop a business model which includes spinning out companies based on intellectual property to which substantial value has been added through this platform and secondly, to create a Foundation."

The creation of the proposed Foundation is unprecedented, he says. "The proposed Foundation will raise money, specifically for innovation in drug discovery and development and basically, seed drug discovery, not just at UCT, but at other African institutions. In fact, wherever there is a good project to support and where we have the necessary platforms. In turn the foundation will have a controlling stake in the Intellectual Property that comes out of any project that they fund."

The Drug Discovery Centre, which will also be known as Holos 3ple-D, will be formally launched during the first week of April 2011.

saving millions of lives. So they know what they're doing! At this point of my career I suspect I take more than I give by serving on the MMV's ESAC, but it really has been an amazing learning curve," Chibale chuckles.

His MMV colleagues have been instrumental in helping him determine the freedom to operate – the first major task to scope when embarking on innovation. "In other words, are there not perhaps other researchers working in the same area who are already further along the innovation chain?" he posits.

This brings him to the next innovation milestone – creating a Target Product Profile or TPP.

"Imagine that you have discovered your products, what is the profile that is going to help? For example, if it's a drug for cancer, how many times is the patient going to take it? Are they going to take it orally? The answers to all these questions determine your approach to dealing with the problem. So you define a TPP."

The next phase involves defining the progression criteria. "In other words, how are you going to proceed from there in terms of the value chain and what are the criteria that will really help you make decisions to move along the value chain?"

Chibale believes this phase is absolutely pivotal and determines the difference between academic research and real innovation. "How well researchers apply their minds to this phase will make a difference to a project's success or failure. You actually must learn to let go of it, if the signs of progress aren't there." He invokes his pet phrase: "Kill quick, kill cheap!"

"The major stumbling block to successful drug development is not actually its efficacy, it's what the body does to the drug" continues Chibale. "You've always got to keep in mind how the patient will metabolise the drug. So you have to think about this early on, when you're defining the Target Product Profile and defining its progression criteria."

Chibale completes his summary of the drug discovery process with the revelation that these steps have accelerated one of his innovation projects. "In less than six months, we achieved something I have never ever seen in my entire career. We have identified novel chemotypes that are unrelated to existing drugs on the market. One of the prioritised and promising series has reached the confirmed lead stage and we are currently pursuing a lead optimisation campaign, to address all identified liabilities with a view to declaring a clinical candidate in the very near future."

"It highlights that taking out a patent at too early a stage is senseless. We never filed a patent until this year when we had entered the lead optimisation stage. That's when we filed!" Chibale exclaims.

Participants and title	Granted Regions	Pending Regions
Chibale, K., Greenbaum, D.C., McKerrow, J.H. Anti-Parasite Compounds and Methods of Their Use.	ZA	–
Chibale, K., Nchinda, A.T., Sturrock, E.D. Angiotensin I-Converting Enzyme (ACE) Inhibitors.	EP, ZA	US, AU, CA
Chibale, K., Nchinda, A.T., Sturrock, E.D. Angiotensin I-Converting Enzyme (ACE) Inhibitors.	ZA	US, EP, CA, AU