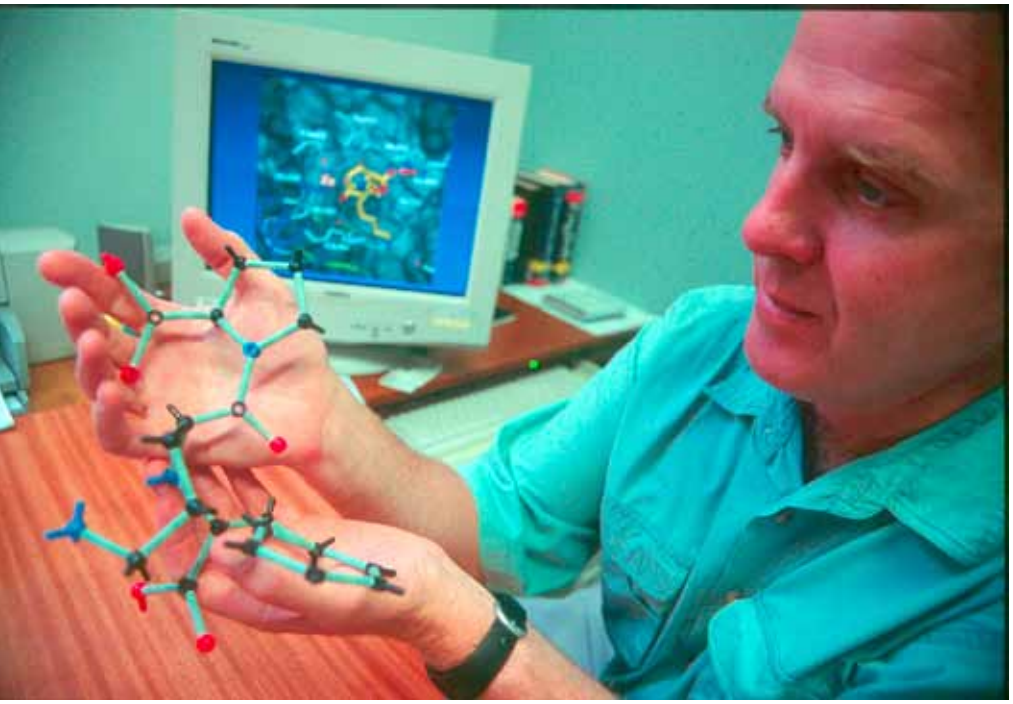
Serial Inventor Sturrock Holds All the ACEs



Having solved a problem that has confounded the scientific community for decades, UCT Professor Ed Sturrock of UCT's Institute of Infectious Disease and Molecular Medicine (IIDMM) is one of UCT's most successful innovators.

A world leader in the field of metalloproteases, Sturrock is internationally renowned for his pioneering work on illuminating an understanding of the human angiotensin-converting enzyme (ACE) – a protein that plays a key role in blood pressure regulation.

Together with his UCT colleague Sylva Schwager and Professor Ravi Acharya and Dr Ramanathan Natesh based at Bath University, Sturrock published the first three-dimensional structure of ACE in Nature in 2003.

Their breakthrough created enormous interest from the international scientific and medical communities at the time, as over the years numerous high-profile research teams had tried – and failed – to map the enigmatic enzyme.

Armed with a better understanding of the peptide and its interaction with its inhibitors, the team of scientists was then able to begin work on developing a new generation of ACE inhibitor drugs. "ACE consists of two parts, the N and C domains, with different functions. Current drugs inhibit both domains," Sturrock explained. "By designing specific domain-selective ACE inhibitors we expect to produce next-generation drugs that are safer and more effective and have fewer side effects."

The current generation of ACE inhibitor drugs, which are widely used to treat cardiovascular diseases, such as high blood pressure, heart failure, coronary artery disease, and kidney failure, as well as other related ailments, has unpleasant, and sometimes dangerous, side-effects. These include a persistent dry cough and swelling of the mouth and upper respiratory tract – termed angioedema – which can be life-threatening.

Using the unique knowledge of the three-dimensional structure of ACE, Sturrock and his collaborators have engaged in the design and synthesis of domain-selective ACE inhibitors and patents have been filed for the C-domain and N-domain crystal structures of the ACE protein and related features, as well as for novel C-domain-selective ACE inhibitors. The IP is presently owned by the Universities of Cape Town and Bath.

"The potential is huge, but the time from breakthrough to presenting new drugs on the market is anything between six and 12 years," Sturrock added.

During 2008 the board of Cape Biotech Trust approved support for the commercialisation of the technology through a spin-out company, AngioDesign Therapeutics Pty Ltd (ADT). Due to various reasons, *inter alia,* the formation of the Technology Innovation Agency, into which CBT was incorporated, this funding arrangement has not been finalised as yet.

But the show is going on. Sturrock says, "At present the work is being done in my laboratory, in Kelly Chibale's laboratory, and at the University of Bath. We're also outsourcing some of the work. So it's a bit of a hybrid in terms of being an industry-academia venture."

"However, in its current form it is a brilliant way of helping students in my group get a real sense of what is involved in innovation and the translation of science from the laboratory to the clinic,"

he adds.

Sturrock explains that the most costly aspect of the drug discovery and the associated development process is the validation of therapeutic targets during clinical trials. ***"ADT aims to short-circuit the process by applying structure-guided drug design to proven disease targets and developing next-generation drugs with superior efficacy and side effect profiles," he says.***

The plan is for ADT to guide the lead ACE inhibitor candidates through phase I clinical trials in order to establish proof of concept and maximize the value of its core intellectual property and technology. ADT then hopes to negotiate licensing and co-development deals with pharmaceutical companies with relevant therapeutic interests.

A UCT alumnus, Sturrock began work on the ACE protein nine years ago at Harvard Medical School while on a Fellowship sponsored by the National Research Foundation (NRF) and National Institutes of Health (NIH). It was at Harvard that he established links with his Bath collaborator – a working relationship that has endured and prospered.

His work at on ACE at Harvard prepared him for his breakthrough a decade later on the three-dimensional crystal structure of the enzyme and the structure-based design and synthesis of novel domain-selective inhibitors.

Sturrock returned to South Africa and UCT in 2007 and set himself the goal of maintaining and developing his contacts with internationally renowned colleagues abroad. "This was particularly important as the skills and technology in protein X-ray crystallography were lacking in South Africa and in the Western Cape," he noted.

Now based at UCT's Institute of Infectious Disease and Molecular Medicine, Sturrock is a Wellcome Trust International Research Fellow. He believes this fellowship has been instrumental in giving him time and space to dedicate to his research. "I think that I have been very fortunate, in that these senior fellowships give academics five years in which to focus on research."

"The conditions allow you to spend only 15% of your time doing teaching and administration. That really gave me the opportunity to do research – to pursue something that I am passionate about and enjoy. What drives me is that one is developing – not just new compounds which could become new drugs – but one is finding out new things about science, about life, and it's really that discovery process that drives me," Sturrock enthuses.

Another major research project Sturrock and his team are working on is related to ACE, but looks more at the processing of the proteins attached to the cell membrane. These molecules are cleaved by another protease and released into the extra-cellular milieu – into the bloodstream in the case of ACE. This process is important, because recent work has shown that the membrane-anchored form is the more physiologically important form.

"We've done quite a lot of work trying to understand that process – how ACE is cleaved off the membrane and to try and identify the protease that is responsible for that cleavage. And this would also potentially be something that could be developed into a therapeutic application – although we are not really at that stage yet with this project. Fortunately we've been able to get a steady stream of publications, and PhD and Masters students out of that work."

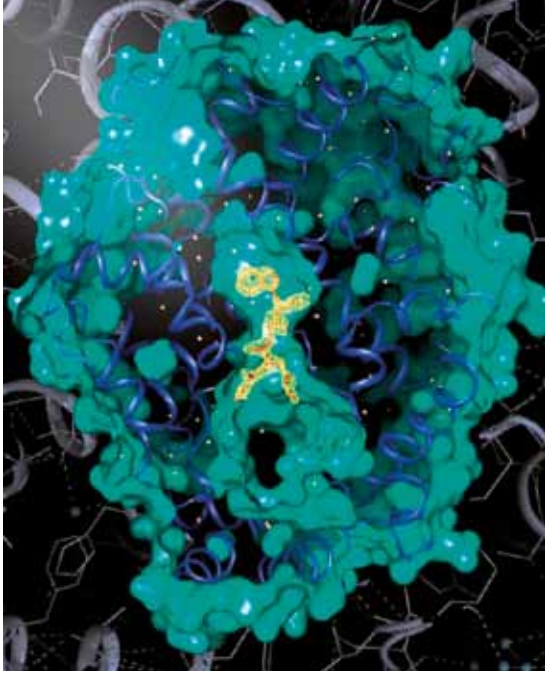
Sturrock and his colleagues' work looks promising. "We have a couple of early lead compounds which are selective for the ACE C-domain Current ACE inhibitors are not domain-specific - so they interact with both – and this causes an increase in a hormone called bradykinin which is largely responsible for the side-effects of these drugs – like the angioedema and the persistent cough.

"Our approach has been to develop inhibitors that block the one domain – the C domain – so that the other domain can nibble away at the bradykinin and bring those levels down and thus improve the side-effect profile."

Sturrock explains that the patenting process can be long and laborious. It took about seven years for the patent on the C domain structure to be granted in Europe and the US patent is still being processed.

Sturrock pays homage to his co-researchers. He says that one of the most important aspects of a research project is developing a team spirit, so that everyone works towards a common goal, sees themselves as part of the same team and can share in the project's successes and failures.

He maintains that the principal investigator's enthusiasm, passion, and ability to deliver relevant outputs,



generates enthusiasm within the research team. He also believes in encouraging collaboration with other groups and participation in local and international conferences, as it all helps to build a spirit of innovation and discovery within the research context.

Sturrock says that he thinks his team is fortunate in being embedded within the IIDMM as it enables them to utilise the skills and technologies of other groups to supplement their own skills sets when it is necessary. For example, he's placed a number of his students either part-time or full-time in Professor Kelly Chibale's Chemistry Laboratory and they work with Chibale's team to supplement their chemistry skills.

Sturrock also acknowledges the assistance and advice he's received from experts and specialists in the pharmaceutical and associated industries. "I think that is really key to have their input – so that we continue with the caliber of research that will result in great drug-discovery.

Title and Inventors	Granted Regions	Pending Regions
Acharya, K.R., Sturrock, E.D. ACE N-Domain Crystal.	ZA	US, AU, CA, EP
Acharya, K.R., Sturrock, E.D. Crystal Structure of an Angiotensin-Converting Enzyme (ACE) and Uses Thereof.	AU, ZA, US, EP, SE, CH, DE, DK, FR, GB, IE, LU, NL, SI, MC, CA	US Div
Chibale, K., Nchinda, A.T., Sturrock, E.D. Angiotensin I-Converting Enzyme (ACE) Inhibitors.	EP, ZA	US, CA, AU
Chibale, K., Nchinda, A.T., Sturrock, E.D. Angiotensin I-Converting Enzyme (ACE) Inhibitors.	ZA	US, EP, CA, AU