Structure of a Glycosylation Mutant of Testis ACE bound to a novel Inhibitor

Jean Watermeyer[a], E.D. Sturrock[a], B.T. Sewell[b], [a]*Division of Medical Biochemistry, UCT, South Africa.* [b]*Electron Microscope Unit, UCT, South Africa.* E-mail: jean@science.uct.ac.za

Human angiotensin-converting enzyme (ACE) is vital to the regulation of blood pressure. ACE inhibitors are commonly used for the treatment of cardiac disease. Structural information about ACE has only been elucidated recently, with the solution of a crystal structure of human testis ACE (tACE)[1].

We have determined the structure of a glycosylation-deficient mutant of tACE, to 2.9 Å. The structure reveals a predominance of α-helices with the active site located deep in the cavity that separates the two sub-domains. This is in agreement with the structure of a native form of tACE that was published recently. We have also solved a structure of human testis ACE in complex with a novel C-domain specific inhibitor, to 3.0 Å, which reveals detailed information on the interactions of this inhibitor with the active site.

In addition, we have carried out a normal mode analysis that reveals the intrinsic flexibility of tACE about its active site cleft. The intrinsic flexibility suggested by this study indicates a mechanism whereby subaccess could be achieved.

The information obtained in this study will be used in the design of new specific inhibitors of the C-domain of somatic ACE.

[1] Natesh R., Schwager S., Sturrock E., Acharya K., *Nature*, 2003, **421**, 551.

Keywords: glycoproteins, metalloprotein structures, drug targets