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Poster presentation

From biochemical and structural studies of soluble guanylate cyclase toward drug design

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The heterodimeric haemoprotein soluble guanylate cyclase (sGC) is the direct sensor and mediator of nitric oxide (NO) signal transduction via the NO-sGC-cGMP pathway. Aberrant sGC-dependent signalling may be fundamental to the aetiology of a wide variety of cardiovascular pathologies. As a consequence, compounds that activate cGMP production by sGC have a considerable therapeutic potential.

To date, x-ray structures of independent sGC domains HNOX, HNOX-A and GC have been solved. Nevertheless, the determination of the full-length sGC x-ray structure would provide additional clues to understand the structural basis for the mechanism of sGC assembly and regulation and should facilitate the design of these therapeutic agents.

To achieve this goal, I developed a heterologous expression system of full-length bovine sGC (Fl-sGC). Early attempts to produce recombinant bovine sGC in *E. coli* resulted in misfolded protein accumulation. Indeed, producing soluble protein in *Escherichia coli* is still a major difficulty in the sGC field. By using fusion technology, I successfully overexpressed both α and β subunits in a soluble heme-bound active form. Optimization of expression levels by varying bacterial growth conditions including temperature, media, additives and induction, will be followed by purification and characterization of Fl-sGC. So, a crucial step has been achieved, allowing us to pursue structural studies to probe the structure and mechanism of sGC and promote the discovery of stimulators of this physiologically important enzyme.