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# Conjoined NO-sensitive guanylyl cyclases

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## Background

NO-sensitive guanylyl cyclases (NO-GC's) that catalyze the reaction of GTP to the second messenger molecule cGMP are heterodimeric enzymes consisting of an α and a $\beta_1$ subunit. The two prevalent isoforms in humans ($\alpha_1/\beta_1$, $\alpha_2/\beta_1$) are time-tested targets for drugs that release nitric oxide (NO) and new compounds that either sensitize the enzyme for activation by NO or activate the enzyme independently of NO. Homologous NO-GC subunits consist of an amino-terminal HNOX domain followed by a PAS- and a coiled coil domain and the carboxy-terminal catalytic domain.

## Results

Measurement of FRET between fluorescent proteins tagged to the amino- and carboxy-terminus of the subunits indicated close proximity between the amino-terminal HNOX domains and the carboxy-terminal catalytic domains of the enzyme. On the basis of these results we constructed conjoined NO-GC's by fusion of the α amino-terminus to the $\beta_1$ carboxy-terminus leading to a monomeric enzyme complex. Surprisingly but in accordance with the FRET results these conjoined NO-GC's ($\beta_1\alpha_1$, $\beta_1\alpha_2$) showed specific enzyme activity and stimulation by NO and various modulators of GC activity.

## Conclusion

These obligate enzyme variants faithfully reproduced the pharmacological properties of the heterodimeric enzymes including an isoform specific differential activation of the NO-independent drug cinaciguat. Novel applications of conjoined NO-GC's including adenoviral gene transfer will be discussed.

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