

## Interaction between steroid hormone receptors and the protein FKBP52: towards new molecular patterns

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In living cells, *cis* to *trans* (i.e.,  $\omega = 0^\circ$  to  $\omega = 180^\circ$ ) amide bond isomerization occurs at specific sites of proteins to allow backbone re-orientations that are essential for biological effects. Such isomerization reactions are reached at a very slow timescale, even in the case of  $\alpha$ -Pro amide bonds, where the rotational energy barrier is strongly decreased. As molecular timers, peptidyl-prolyl isomerase (PPIase) enzymes are able to accelerate  $\alpha$ -Pro isomerization to rapidly converge towards specific biological effects.

The 52 kDa immunophilin FKBP52, which contains an N-terminal PPIase FK1 domain, is known to participate in the expression and in the processing of steroid receptors (SRs). Although its PPIase activity is not essential for receptor regulation, the FKBP52 FK1 domain interacts directly with the ligand-binding domain of the unliganded SRs to stabilize the SR / Hsp70 / Hsp90 / p23 complex and / or to modify ligand affinity.

With respect to the identified interaction between the FK1 domain of FKBP52 and a  $\beta$ -turn of the human estrogen receptor  $\alpha$  (ER $\alpha$ ) located in its ligand-binding domain, we engaged in a "bioinspired" approach consisting of the synthesis of peptidic and peptidomimetic modulators derived from this interacting ER $\alpha$   $\beta$ -turn and containing the sequence K<sup>363</sup>RVPGFVD<sup>370</sup>, where the turn motif is centered on the PG motif. In this study, we adopt the technique of NMR in order to design and test new peptidomimetics as inhibitors of the PPIase activity of the FKBP52 FK1 domain and, therefore, as competitive binders of FKBP52 protein partners.

[1] Cillian Byrne et al. *Biochemistry*, **2016**, 55, 5366-5376