Supporting information for:

Structural study of a flexible active site loop in human indoleamine 2,3-dioxygenase and its functional implications.

Lucía Álvarez[1,2], Ariel Lewis-Ballester[3], Adrián Roitberg[4], Darío A. Estrin[1,2], Syun-Ru Yeh[3,] Marcelo A. Marti[,5,6], Luciana Capece*[,1,2]*

[1]Dto. de Química Inorgánica, Analítica y Química Física, Fac. de Ciencias Exactas y Naturales, Univ. de Buenos Aires, Buenos Aires, C1428EGA, Argentina. [2]INQUIMAE-CONICET, Buenos Aires, C1428EGA, Argentina, [3]Department of Physiology and Biophysics, Albert Einstein College of Medicine, 1300 Morris Park Avenue, New York, NY 10461, USA, [4]Department of Chemistry, Quantum Theory Project, 440 Leigh Hall, University of Florida, Gainesville, FL. 32611-7200, USA. [5]Dto. de Química Biologica Fac. de Ciencias Exactas y Naturales, Univ. de Buenos Aires, Buenos Aires, C1428EGA, Argentina [6]IQUIBICEN-CONICET, Buenos Aires, C1428EGA, Argentina.

1.1 JK-loop structural modeling

The structural alignment between hIDO (PDB code 2D0T), xcTDO (PDB code: 2NW8) and PrnB (PDB code: 2X67) is shown in figure S1.

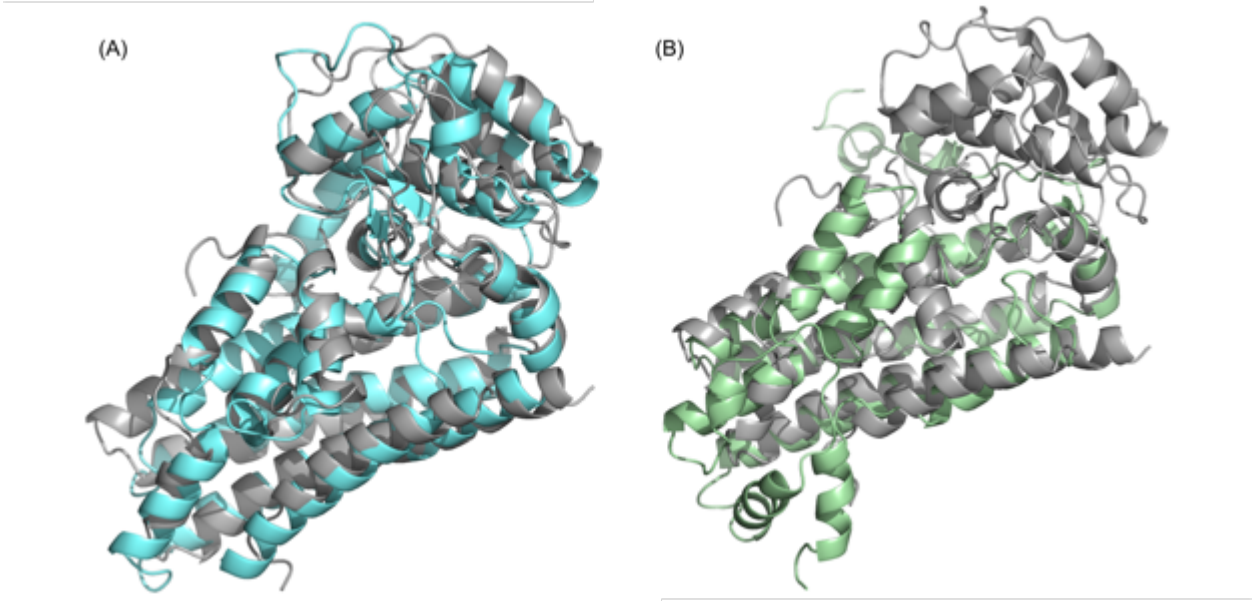

Figure S1. The hIDO crystal structure (2D0T) in gray aligned with a) the crystal structures of PrnB (PDB code: 2X67) in cyan and b) xcTDO (2NW8) in green.

Sequence comparison of hIDO, PrnB, and xcTDO.

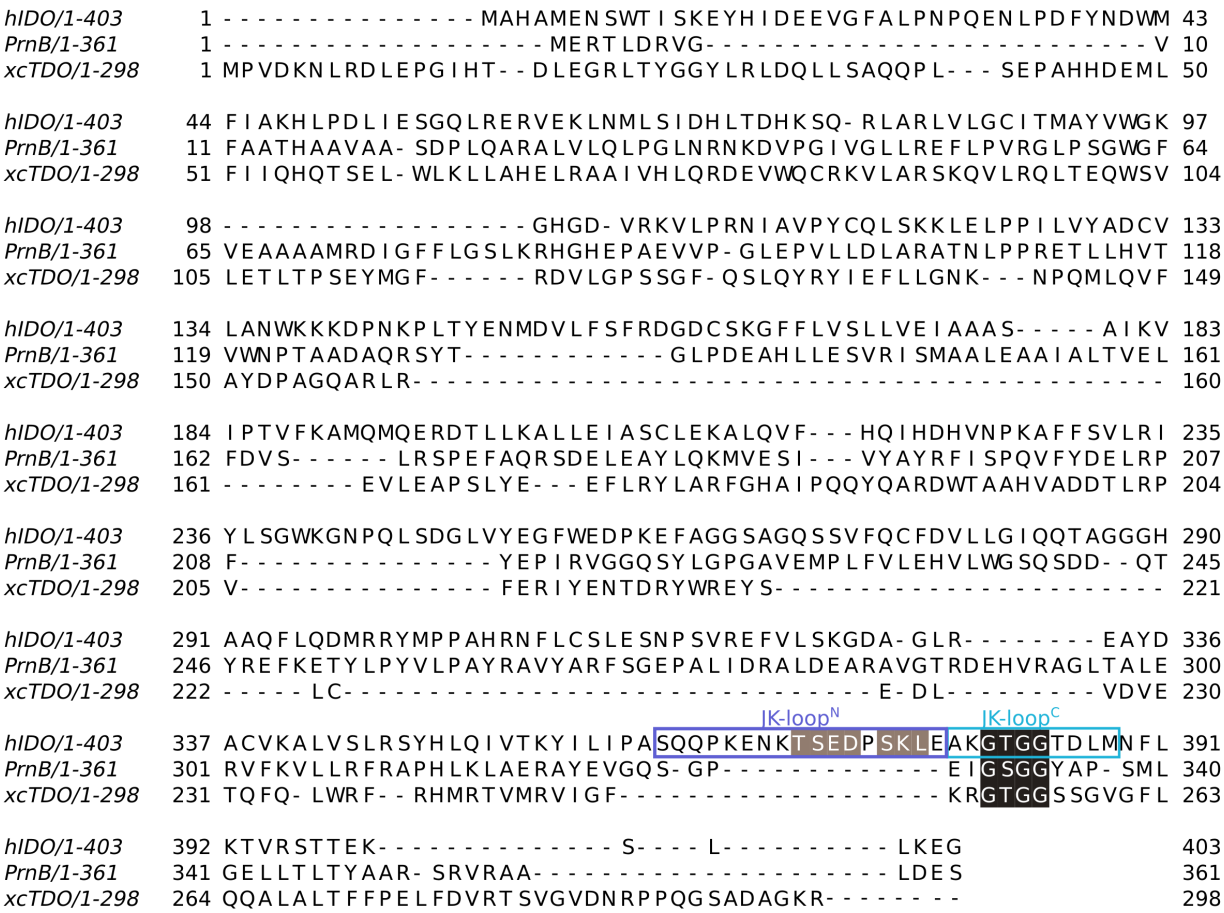

Figure S2. . Sequence alignment of hIDO, PrnB, and xcTDO. The GT(S)GG motif and the SKL and TSED phosphorylation site are highlighted in green and red, respectively.

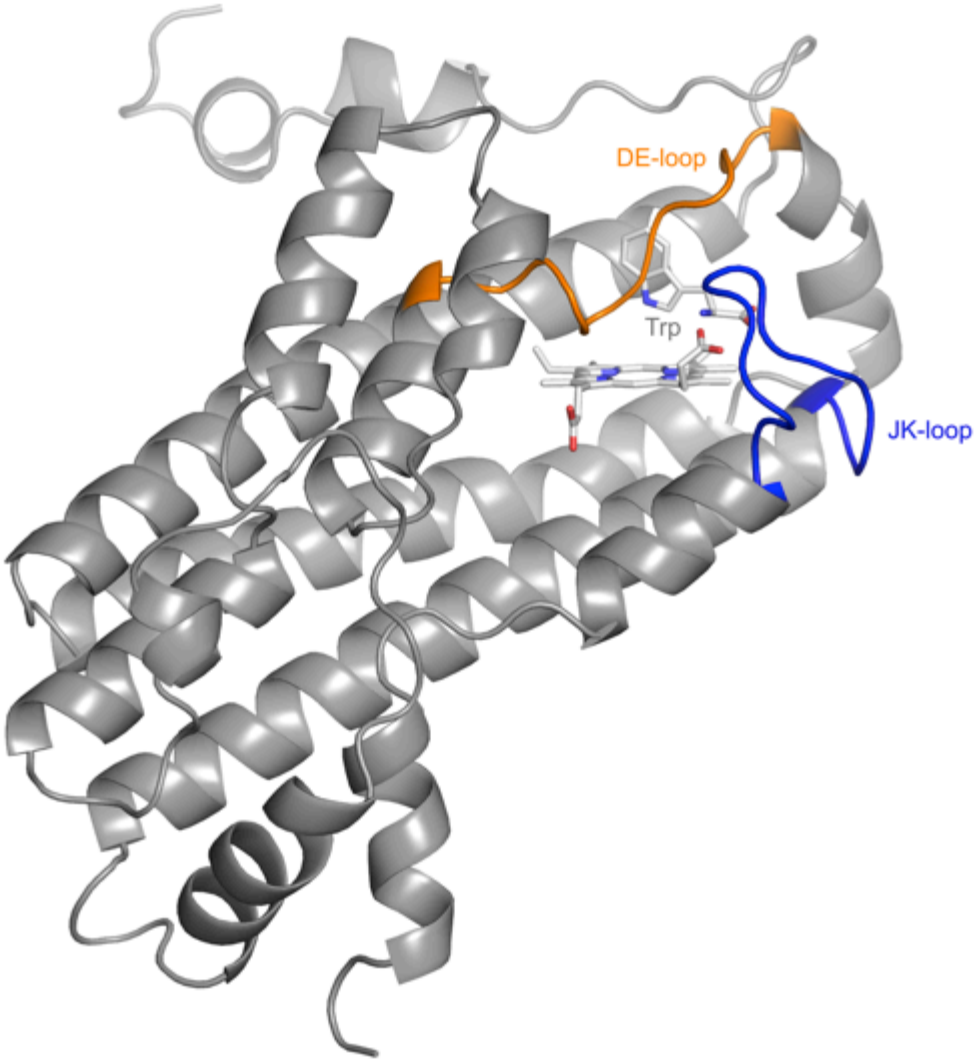

Figure S3. xcTDO structure, where the JK-Loop connecting the J-Helix and K-Helix is shown in blue. The Trp position resembles the conformation 1 (Cf1) in hIDO . The DE-loop is highlighted in orange.

1.2 JK-Loop Structure and Dynamics.

Table S1 shows the population of each JK-Loop^{C} state for each of the three T-REMD simulations, SF-hIDO, Cf1-hIDO and Cf2-hIDO clustering based on the residues that belong to the JK-Loop^{C}.

Table S1. Population of each JK-Loop^{C} state in SF-hIDO, Cf1-hIDO or Cf2-hIDO trajectories.

JK-Loop^{N} state	State Population		
	SF-hIDO	Cf1-hIDO	Cf2-hIDO
Closed	96.6	99.9	-
Intermediate	1.8	-	49.7
Open-extended	1.6	0.1	50.3

3. Detailed structural and functional characterization of JK-Loop conformational states.

Table S2. Comparison of the interactions involving the Trp and the main residues of the active site in the wild type protein and the T379A mutant.

Interactions		Cf1 wt*	Cf1 T379A*
R231 HH12**	Trp OXT	99.9	62.2
R231 HH22**	Trp O	86.6	49.9
R231 HH21**	Trp O	-	85.0
R231 HH22**	Trp OXT	7.2	42.3
R231 HH12**	Trp O	0.1	37.4
T/A379 H	Trp O	91.0	48.1
T379 OG1	Trp-NH3 group	63.3	-
T/A 379 H	Trp- Oxt	-	31.3
Heme group - O2	Trp -NH3 group	69.8	47.5
Gly 262 O	Trp- NH3 group	-	34.8

***The values are expressed the occupancy percentage of hydrogen bonds averaged over simulation time,

**The critical hydrogens in R231 are defined in Fig. S4.

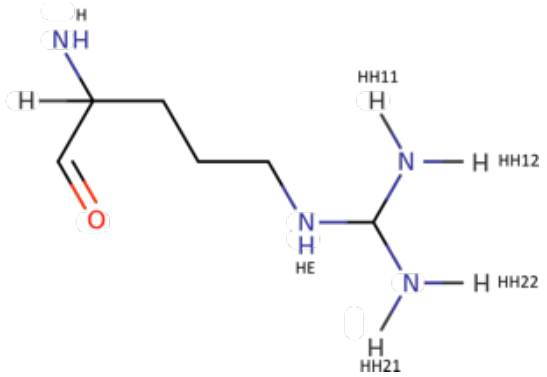

Figure S4. Naming system of the Hydrogen Atoms of the R231.