DEVELOPMENT OF AN INHIBITOR FOR THE S53L MUTANT OF PROTEIN KINASE PKACβ INVOLVED IN THE CUSHING SYNDROME

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Mutations in the gene encoding the protein kinase A (PKA) leads to the Cushing disease, a cortisol producing adenoma [1]. This rare disease is manifested by brain dystrophy and other symptoms. PKA has 3 isozymes of its catalytic subunit (PKACα, PKACβ and PKACγ). The mutation about which we are talking here is observed in the gene of PKACβ [2]. In effect, we have performed the first characterization of PKACβ and its mutant with several of ARC-inhibitors (nucleotide-oligopeptide conjugates). The inhibitors previously developed against PKACα activity work better with PKACβ.

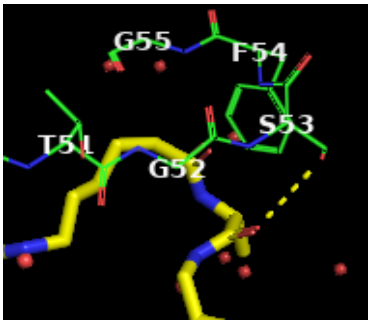

Fig. Interaction of ARC-1039 (yellow) with Ser53 of PKACA (green).

In drug design, crystal structure analysis is performed to map interactions and obtain potent compounds. Actually, there are no data on the structure neither for PKACβ nor for its S53L-mutant, making the inhibitor design tougher. We have resolved the structures of complexes of PKACα and ARC-inhibitors. They point to the interaction of the hydroxyl of Ser53 with specific moieties of ARC-inhibitors (see Fig.). Moreover, we worked on the development of selective inhibitors towards the mutant PKACβ using different strategies to disrupt the H-bond of Ser53 with them.

Given that AMTH [5-(2-aminopyrimidin-4-yl)-thiophene-2-carboxylic acid moiety] and Ahx ["6-aminohexanoic acid moiety], ARC-1463 (AMTH-Ahx-D-Trp-NH_2) and ARC-1427 (AMTH-Ahx-D-Trp-Ahx-$(D\text{-}Arg)_6$-D-Lys-NH2) have selectivity coefficients of 2.13 and 0.7 towards S53L-PKACβ, respectively. ARC-1463 has KD values of 21 nM (PKACβ) and 10 nM (S53L-PKACβ), while ARC-1427 has 16 pM (PKACβ) and 23 pM (S53L-PKACβ). Finally, further studies will include the co-crystal structures to establish the exact binding mode of the inhibitor to the kinase.

References

1. N. Luzi et al., **2018**, *FEBS Open Bio 8, 606–613*
2. S. Espiard et al., **2018**, JCI Insight. 3(8):e98296

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