The role of flexibility in Drug Binding

Madrid, January 16th, 2012 - Angewandte Chemie International Edition publishes a communication by CNIO investigators Julen Oyarzabal and Francesco L. Gervasio on the mechanism by which drug binds to flexible anticancer target. Our understanding of the mechanism by which drug bind to their targets has evolved from a static lock-and-key concept, where only the drugs with the “right shape” can dock to their biological targets, to a dynamic one. Within this dynamic framework, two limiting mechanisms have been proposed: conformational selection and induced fit. The first implies that already in the unbound form both the target and the ligand can assume the right shape to dock. In the induced fit hypothesis, the ligand induces the target protein to assume conformations that are virtually inaccessible to the unbound-form.

In “Conformational Selection versus Induced Fit in Kinases: The Case of PI3K-γ”, CNIO’s investigators have shown that, in the case of the important anticancer drug PI3K-γ, both mechanisms are at work, meaning that the PI3K-γ is able to assume the right general shape to bind to its inhibitors but also that the inhibitors play an active role in shaping the binding cavity.

This advance in our understanding of the mechanism by which drug bind to their targets could lead to the rational design of a generation of more selective anticancer drugs with less side effects.

Conformational Selection versus Induced Fit in Kinases: The Case of PI3K-γ†

Dr. Marco D’Abramo¹, Dr. Obdulia Rabal²,³, Dr. Julen Oyarzabal²,³, Dr. Francesco Luigi Gervasio¹, Angewandte Chemie International Edition 51, 642-646, 2012