Discovery and development of small-molecule PPIs inhibitors by computational and biophysical tools

N. Dotan, N. Ruimi, E. Ratzon, E. Cohen, I. Bloch and M. Gal

Migal - Galilee research center, Kyriat Shmona, Israel, **MaayanG@migal.org.il**

Protein-Protein Interactions (PPIs) play a critical role in regulating many cellular processes. However, finding novel PPI inhibitors that interfere with specific binding of two proteins and has a therapeutic potential is considered a great challenge, mainly due to the complexity involved in characterizing multi-molecular systems and our limited understanding of the biophysical principles governing PPIs. As of today, the arsenal of tools for finding a new small molecule inhibitor of PPIs is rather limited and is commonly done by separate procedures of either in-vitro or in-silico screening techniques. NMR and biophysical tools are among the few biophysical methods capable of either screening for PPI inhibitors or serve as a secondary tool complimentary to the chosen high throughput method.

Here we will focus on two imperative biological systems where the screening for small-molecule inhibitors was driven by biophysical and computational tools, the PD-1:PD-L1 and MDM2-p53 proteins interaction. The first system is an important checkpoint receptor in T-cell regulation, and the latter inhibits the activity of the tumor-suppressor p53 and is targeted for anti-cancer therapeutics. Novel and unprecedented small molecules targeting these systems will be described.

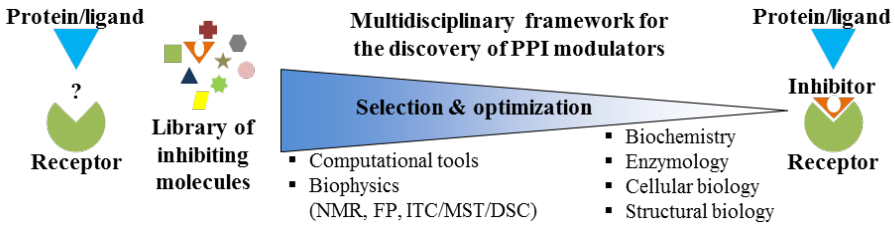

Figure 1: the identification of PPIs inhibitors by computational and biophysical tools