Polypharmacology in Cancer Therapy

Ihsan Muchsin

Student of Master Programme of Life Science Informatics

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Polypharmacology

- Polypharmacology: The design or use of pharmaceutical agents that act on multiple targets or disease pathways
- Consideration: Cost-effective, better efficacy, better safety
- Polypharmacology is relevant for complex diseases, for example, cancer and CNS diseases

Cancer

- Cancer is a group of diseases characterized by abnormal cell growth with the potential to invade or spread to other parts of the body
- Involving wide target networks and cellular pathways
- Promising targets for polypharmacology approach: protein kinases and Hsp90

Protein kinases

- Protein kinases: enzymes that modifies other proteins by phosphorylation
- The human genome contains about 500 protein kinase genes
- Protein kinases are involved in multiple cellular pathways and networks
- An example of protein kinase: PI3K, Akt

Nelfinavir

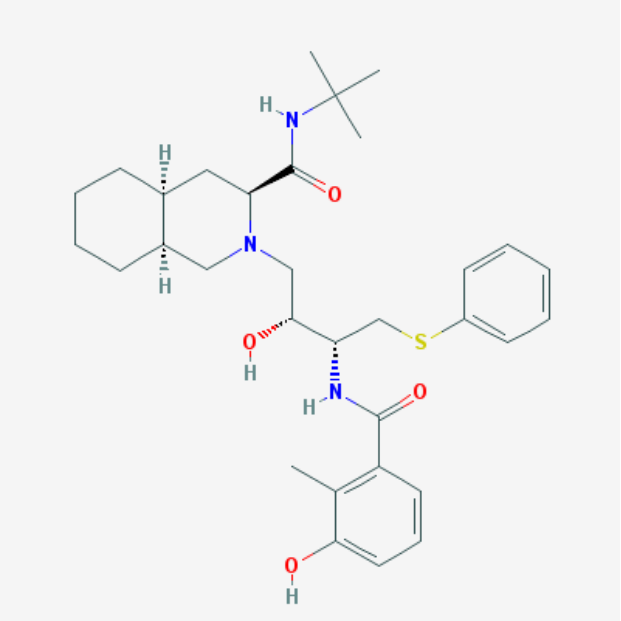

Figure 1. 2D structure of Nelfinavir

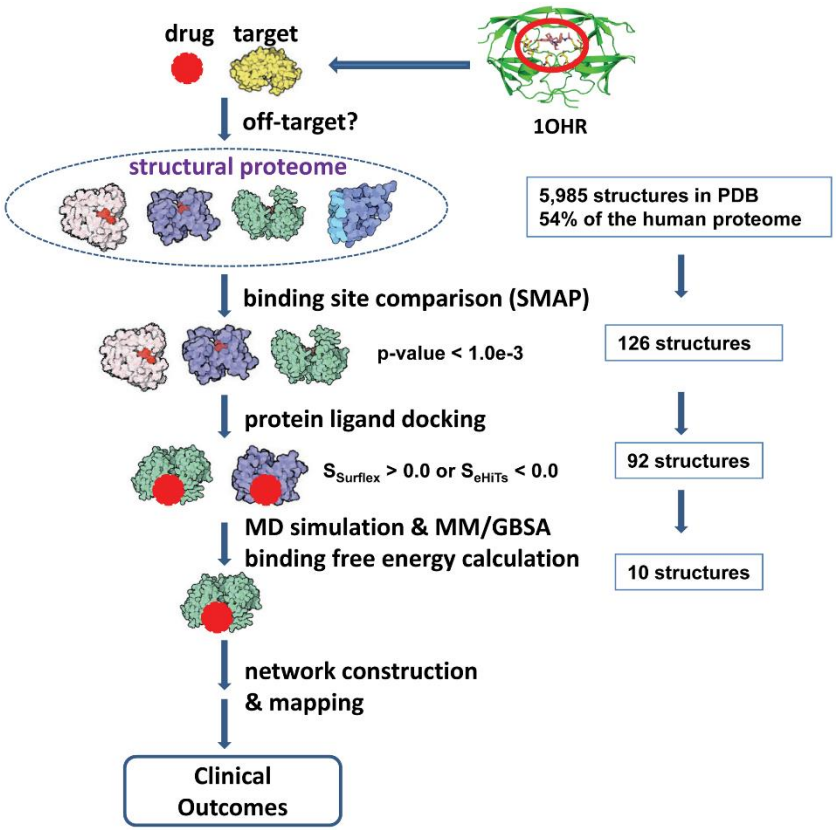

Figure 2. The structural proteome-wide off-target pipeline

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Nelfinavir cont.

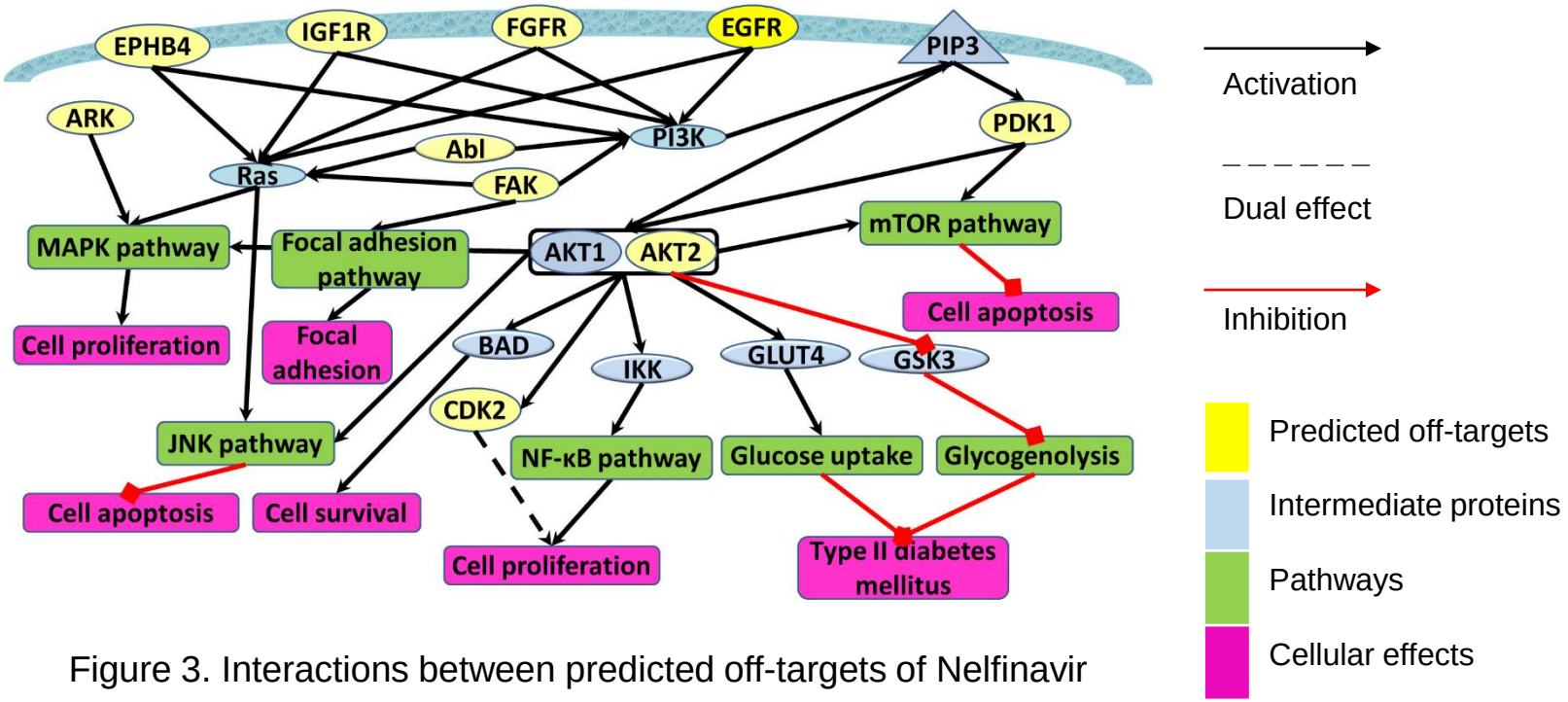

Figure 3. Interactions between predicted off-targets of Nelfinavir

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Hsp90

- A chaperone protein involved in protein folding, protein stabilization against heat stress, and protein degradation
- Tubulin is an Hsp90 client protein which is also a main target of cancer drug
- A single molecule that simultaneously inhibits Hsp90 and one or more of its client proteins could improve efficacy

Hsp90/tubulin dual inhibitors

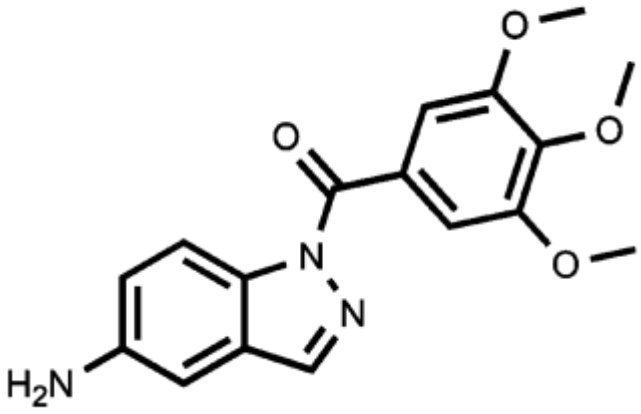

Figure 4. MDG892

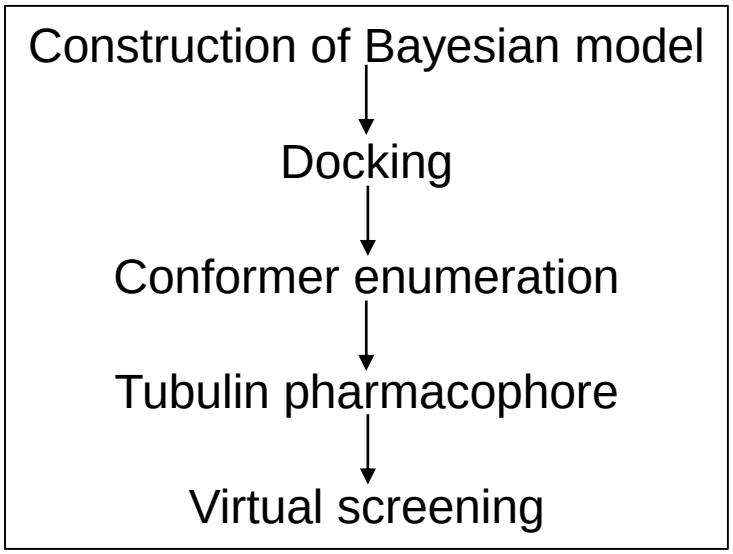

Figure 5. Virtual screening procedure

Conclusion

- Target: A protein / A group of proteins involved in wide range of biological process related to cancer
- Problem: Selecting the optimal target combinations

References

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References

Figure 1:

https://pubchem.ncbi.nlm.nih.gov/compound/nelfinavir

Figure 2 & 3:

Xie, L., Evangelidis, T., Xie, L., & Bourne, P. E. (2011). Drug discovery using chemical systems biology: weak inhibition of multiple kinases may contribute to the anti-cancer effect of nelfinavir. *PLoS Comput Biol*, *7*(4), e1002037.

Figure 4 & 5:

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