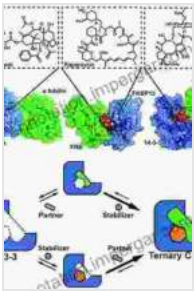
Unlocking the Power of Small Molecules: Targeting Protein-Protein Interactions for Therapeutic Breakthroughs

Protein-protein interactions (PPIs) play a critical role in virtually every biological process, from cell signaling and metabolism to immune responses and disease progression. Dysregulated PPIs are implicated in a wide range of human diseases, including cancer, neurodegenerative disFree Downloads, and autoimmune conditions. Consequently, targeting PPIs with small molecules has emerged as a promising therapeutic strategy.

Challenges in Targeting PPIs with Small Molecules

Developing small molecule PPI inhibitors is a challenging endeavor due to the complex and dynamic nature of PPIs. PPIs often involve large and flat interfaces with shallow binding pockets, making it difficult to design small molecules that can effectively disrupt the interaction. Additionally, many PPIs occur in a cellular context, where they are influenced by a host of other proteins and cofactors.



Targeting Protein-Protein Interactions by Small Molecules by David Brennan

4.3 out of 5

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Screen Reader	: Supported
Enhanced typesetting	: Enabled
Print length	: 535 pages

Strategies for Targeting PPIs with Small Molecules

Despite the challenges, several strategies have been developed to target PPIs with small molecules. These strategies include:

- **Fragment-based drug design:** This approach involves screening small molecule fragments against the PPI interface and then growing them into larger, more potent inhibitors.
- **Virtual screening:** Computational methods are used to identify small molecules that have the potential to bind to the PPI interface.
- **Peptidomimetics:** Small molecules that mimic the structure of peptides can be designed to disrupt PPIs.
- **Allosteric inhibitors:** These small molecules bind to sites on the protein that are distant from the PPI interface and disrupt the interaction indirectly.

Success Stories

Several small molecule PPI inhibitors have been successfully developed and approved for clinical use. These include:

- **Imatinib (Gleevec):** A tyrosine kinase inhibitor used to treat chronic myeloid leukemia.
- **Erlotinib (Tarceva):** An epidermal growth factor receptor inhibitor used to treat non-small cell lung cancer.

- **Crizotinib (Xalkori):** An anaplastic lymphoma kinase inhibitor used to treat non-small cell lung cancer.

Future Directions

The field of small molecule PPI inhibition is rapidly evolving. New technologies and approaches are being developed to overcome the challenges associated with targeting PPIs. These include:

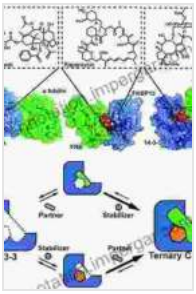
- **Proteolysis-targeting chimeras (PROTACs):** These small molecules recruit E3 ubiquitin ligases to PPIs, leading to the degradation of one of the proteins involved in the interaction.
- **Molecular glues:** These small molecules bind to both proteins involved in a PPI and stabilize the interaction, preventing its disruption.
- **Multivalent inhibitors:** These small molecules bind to multiple sites on a protein, increasing their affinity and specificity for the target.

Targeting PPIs with small molecules is a promising therapeutic strategy for a wide range of human diseases. Despite the challenges, several successful PPI inhibitors have been developed and approved for clinical use. As the field continues to evolve, new technologies and approaches are being developed that hold the potential to further expand the therapeutic applications of small molecule PPI inhibitors.

Further Reading

- Targeting Protein-Protein Interactions for Drug Discovery

- Small Molecule Inhibition of Protein-Protein Interactions: Progress, Challenges and Future Directions
- Targeting Protein-Protein Interactions with Small Molecules: Successes, Challenges and Future Perspectives



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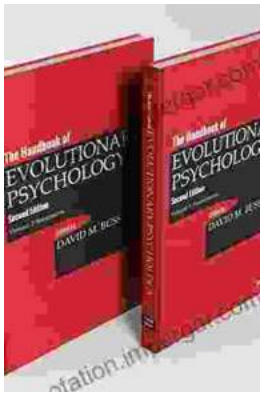

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