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Opinion Article

Resurgence of Targeted Dosage of Covalent Drugs in Pharmacology

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DESCRIPTION

Covalent inhibitors are considered as an important factor in drug discovery and therapy. This field has evolved significantly since the first appearance of covalent inhibitors in the late 18th century, and today about 30% of drugs on the market are covalent inhibitors. The many advantages of covalent inhibitors negate initial concerns about potential off-target toxicity. As such, ongoing research has been reported specifically for cancer targets. Small molecule drug design has traditionally been based on their ability to interact with biological targets in equilibrium binding conditions. These binding states occur in rapid and reversible processes that influence the duration of therapeutic response. Therefore, increasing the duration of interaction between a drug and its target can prolong the therapeutic response. This type of long-lasting interaction can be achieved with covalent inhibitors. Covalent inhibitors bind to targets in two steps, beginning with equilibrium bond formation and ending with covalent bond formation. Covalent drugs have proven to be effective therapeutics for a variety of indications, but are often considered when initiating targeted drug discovery projects, primarily due to safety concerns. There is a need to re-evaluate this important class of drugs and bridge the gap between the historical success of covalent drugs and the reluctance of most drug discovery teams to add them to their arsenal.

Covalent drugs block protein function by forming specific bonds between ligands and target proteins. Covalent mechanisms of action can offer many pharmacological advantages over reversible mechanisms of action. These benefits include increased potency, increased selectivity, and extended duration of action. As a therapeutic class, covalent drugs have a significant impact on human health, as evidenced by the many examples of covalent drugs approved by the US Food and Drug Administration (FDA) for various indications. Many of the approved covalent drugs were discovered by serendipity. Computational drug design has provided a predictable means of creating a new generation of covalent drugs called targeted covalent inhibitors. Several targeted covalent inhibitors are in late-stage clinical development and have shown promising efficacy.

In recent years, it has been recognized that the different potencies of covalent and non-covalent drug modes of action can be combined by designing compounds that combine carefully tuned reactivity with specific complementarity to the target. This concept has a long history of success in the form of mechanism-based or suicide inhibitors that directly target catalytic nucleophiles within the active site of enzymes. To bind to an enzyme, receptor, or transporter, the drug must have a specific structure to "fit" into the protein. Additionally, proteins are in conformations or 3-D shapes that allow the formation of bonds between proteins and drugs. For a drug to work, it must be drawn to its target. Drugs are attracted to their receptors by intermolecular forces. After these forces draw the drug to its receptor, it is also important to keep the drug bound to the receptor for some time sufficient to cause biological changes within the organism.

Covalent small-molecule drugs offer more desirable therapeutic properties than non-covalent drugs for treating difficult diseases. However, the potential of covalent protein pharmaceuticals remains untapped, as proteins cannot be covalently attached to their targets. There is a need to re-evaluate this important class of drugs and bridge the gap between the historical success of covalent drugs and the reluctance of most drug discovery teams to add them to their arsenal.

Drugs with covalent mechanisms of action have the advantage of improved potency, selectivity, and *in vivo* efficacy. Historically, the only covalent drugs on the market were covalent small molecules. Many drugs in current use are covalent inhibitors, irreversibly inhibiting their targets. From a pharmacokinetic point of view, covalent inhibition has many advantages. However, until recently, most organizations avoided designing covalent bonds for fear that non-specific inhibition of off-target proteins could lead to toxicity risks. There is renewed interest in covalent modifiers as potential drugs due to their potential to be obtained. Therefore, it is important to know the reactivity of warheads so that the least reactive warhead can be selected to

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avoid toxicity. A robust NMR-based assay was developed and used to measure the reactivity of various covalent warheads towards the two most common targets of covalent drugs, serine, and cysteine.