Covalent Chemistry Platform for Diagnostics and Drug Discovery

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Overview

delivery and activation of drugs or probes is of great importance in therapeutics, diagnostics, and research. For instance, selective delivery/activation of anti-cancer drugs to tumor cells is crucial for their efficacy and reduced side effects. However, achieving site-selective delivery/activation is challenging and not always feasible with currently available chemical tools. The group of Dr. Nir London developed a chemical platform that uses covalent chemical inhibitors as a targeting system for releasing anti-cancer drugs and probes. This method can be harnessed for numerous therapeutic applications such as improving selectivity and reducing side effects of known drugs, as a platform for screening and development of new drugs, as well as for diagnostic applications and imaging tools.

Background and Unmet Need

Targeted delivery and/or activation of small molecules that serve as drugs or molecular probes is of great importance for numerous applications in medicine, diagnostics, and research. Current chemical strategies for site-selective delivery/activation rely on physiological-based triggers, which are largely nonspecific since they exist ubiquitously in the body. Therefore, the development of targeted delivery strategies with more selective triggering events is of great need.

The Solution

Dr. Nir London and his team have developed a chemical method that harnesses covalent bonds formed between enzymes and covalent inhibitors as a triggering event for the targeted release of potent anti-cancer drugs and chemical probes.

Technology Essence

Dr. Nir London and his team have developed a chemical platform to convert acrylamide covalent inhibitors into targeting systems that upon the formation of a covalent bond with their cognate target protein release a cargo that can be a drug, a fluorophore, or a toxin. This platform, termed CoLDR (covalent ligand-directed release), allows for precise control of releasing cargo only in cells expressing the target protein. The team provides examples showing the technology can be used with several clinical covalent inhibitors (ibrutinib, afatinib, sotorasib) and with a variety of cargos (fluorophores, luminophores, chemotherapies, and targeted drugs). The team demonstrated the efficiency of this method in several applications, including therapeutics, diagnostics, and chemical biology. Specifically, a fluorescent probe was turned on upon binding of the inhibitor (Afatinib) to its target protein (EGFR), thus serving potentially as a research tool. In a different setup, a known covalent inhibitor of a cancer-related enzyme was conjugated to a chemiluminescent probe and was successfully used as a reporter system in a high

throughput screen (HTS) to identify novel inhibitors for this enzyme. This method can also be employed to deliver drug combinations, by combining two known drugs such that the release/activation of one is dependent on the binding of the other drug to its target, thereby creating dual “synthetic lethal” inhibitors. Noteworthy, the method can also be used in “Reverse CoLDR” mode, to label specific proteins of interest while keeping their activity intact.

Applications and Advantages

- Site directed drug delivery
- Combinatorial drug delivery to improve selectivity and reduce side effects
- Delivery of toxin payloads
- Optimization of approved covalent inhibitors
- Diagnostics
- Non-invasive Imaging
- The reactivity is tunable
- Improved selectivity

Development Status

Proof of concept was achieved using several covalent inhibitors with a verity of cargos. The group demonstrated this technology works in vitro and in cells using drugs, fluorescent and chemiluminescent probes. The method was also successfully used in vivo as an imaging tool by injecting luminophores that selectively light up lymph nodes in mice1.

References

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