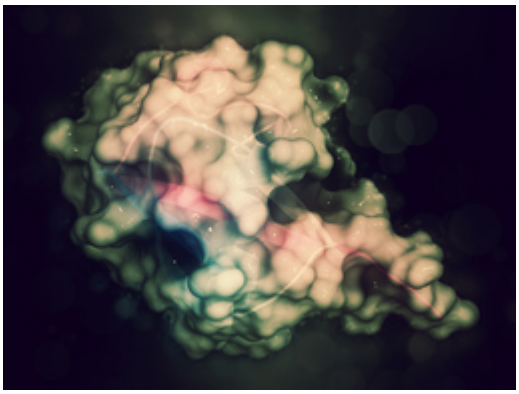
INNOVATION PARTNERSHIPS
UNIVERSITY OF MICHIGAN

Selective Kinase Degraders (PROTACs) for Oncology

TECHNOLOGY NUMBER: 2022-262



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Category
Therapeutics and Vaccines
Life Sciences

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OVERVIEW

Novel proteolysis targeting chimeras (PROTACs) which are potent degraders of kinases

- PROTACs that efficiency cause degradation of proto-oncogenes such as Abl, p38, and c-Src
- Treatment prospects include bladder cancer and other c-Src influenced neoplasms

BACKGROUND

Protein kinases (PK) are enzymes that normally add phosphates to other molecules such as sugars and proteins. PK actions are critical to cellular functions, as evidence by the fact that some of them remain highly conserved in their structure across all eukaryotic cells. More than four hundred diseases have been linked to aberrant activity of protein kinases, including abnormal inflammation, diabetes, and cancer. The identities of several specific protein kinase dysfunctions have been elucidated, though pharmacologic inhibition of these enzymes has not uniformly led to clinical responses. Proteolysis targeting chimeras (PROTACs) have recently emerged as a compelling technology to degrade target proteins using a small molecule entity. PROTACs show a unique mechanism of action which can be used to address resistance to existing therapies, though a need exists for additional research to define the role of protein kinases more fully in diseases such as cancer.

INNOVATION

Researchers at the University of Michigan have developed a series of efficacious small molecule degraders that serve as kinase inhibitors, and which are more active than existing agents. These

novel proteolysis targeting chimeras (PROTECS) are potent degraders for kinases that act as proto-oncogenes, such as Abl, p38, and c-Src. The optimized PROTACs significantly degrade c-Src and are potent in cell culture against a panel of bladder and breast cancer cell lines. In vivo, the PROTAC compounds can be delivered through intravenous or intraperitoneal routes, and an oral formulation is being developed. Beyond the potential use of this agent for treatment, further study using proteomics and genomic sequencing may provide an understanding of those processes that lead to acquired resistance, therefore aiding development of companion drugs. The goal will be to develop pharmacologically active compounds that degrade c-Src and prevent progression of MIBC and other cancers that depend upon deregulation of c-Src for growth.