Exploring innovative approaches to anticancer strategies and pathways

A look into innovative approaches to strategies and pathways to fight cancer

The need for new therapeutic approaches remains high[1]

Despite advancements in oncological and hematological therapies, there is potential for improvement.[2] Five-year survival rates remain low for some cancers.[3]

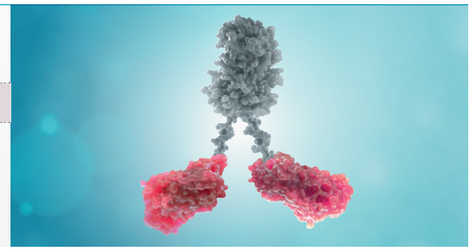
Advancements are needed to address unmet needs across solid tumor and hematologic malignancies.[1,4,5]

BMS is researching innovative approaches with the goal of improving the therapeutic potential of anticancer strategies*

Antibody enhancements

mAbs | NF mAbs | ADCs | Bispecific ADCs

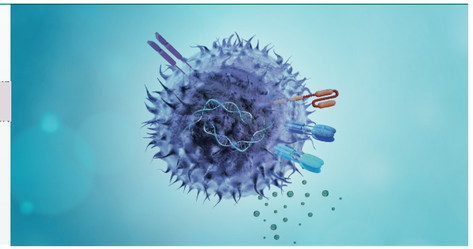
Certain cancer treatments may lack tumor selectivity and lead to a suboptimal risk-benefit profile.[6]



Directed immune activity

BsAbs | CAR T cells

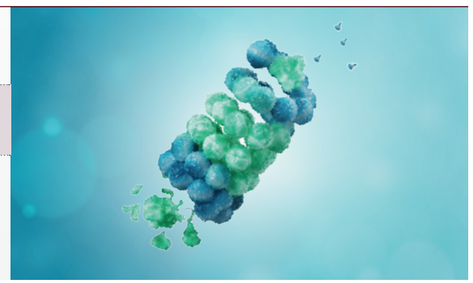
An immunosuppressive tumor microenvironment may limit the immune response necessary to eliminate tumor cells.[7,8]



Novel protein-targeted approaches

Targeted protein degraders | Novel macrocyclic molecules
Potent small molecules | Synthetic lethality

There are several key contributors to oncogenesis that are difficult to target and can cause further disease progression.[9-12]



*Not a comprehensive list of investigative strategies.

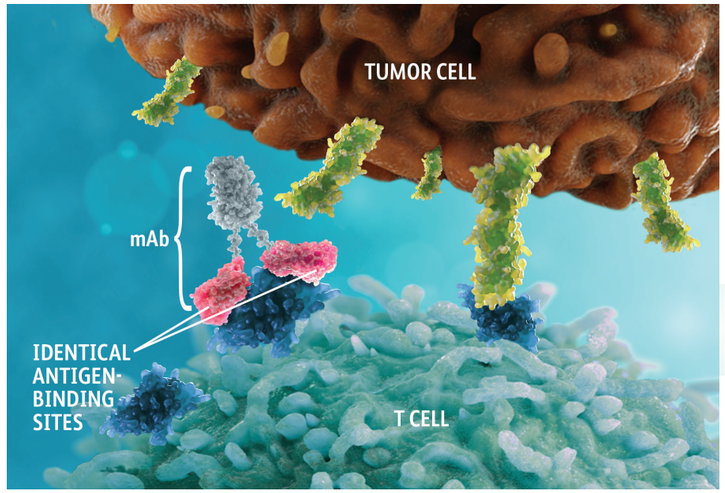
BMS is exploring innovative approaches to anticancer strategies and pathways, alone and in combination, to fight cancer

Antibody enhancements

Antibodies are versatile platforms for therapeutic development and can lead to a variety of approaches that may expand the potential of targeted therapy.[13]

Certain cancer treatments may lack tumor selectivity and lead to a suboptimal risk-benefit profile; there is also potential to optimize the cytotoxic and immune-mediated antitumor activity of mAbs.[6]

Monoclonal antibodies may provide a pathway for selectivity[13]

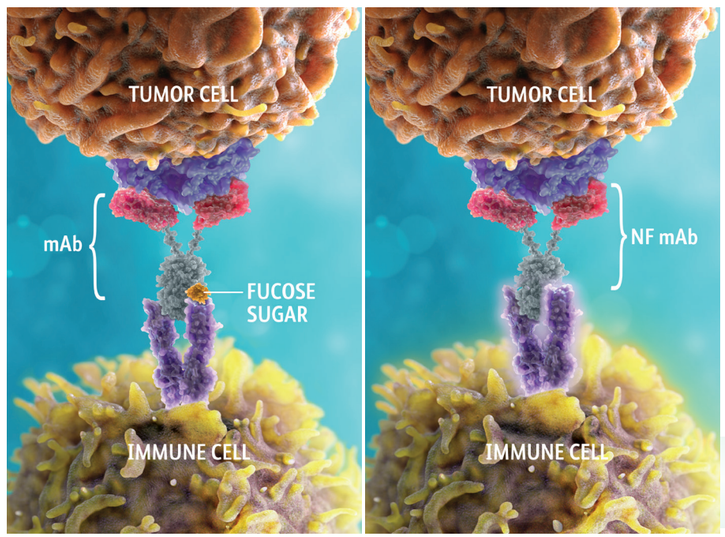


- mAbs may selectively target cells via specific surface antigens, potentially limiting systemic exposure and causing a blockade of protein interactions essential to proliferation[13]
- Studies suggest mAbs can be modified to potentially enhance antitumor activity and/or safety profiles[13]

SELECT INVESTIGATIONAL PATHWAYS

CTL-4, PD-1, and LAG-3

Preclinical research suggests non-fucosylated (NF) mAbs may enhance interactions with immune cell receptors to produce a stronger immune response[14]



- mAbs may link receptors on immune cells to antigens on the surface of tumor cells, targeting tumor cells for cellular effector functions[15,16]
- The presence of a specific sugar (fucose) on the Fc domain of a mAb may hinder the binding strength with immune cell receptors, leading to reduction in cellular effector functions[15]
- Preclinical research suggests NF mAbs may potentially improve cytotoxic activity, providing a more potent immune response than fucosylated mAbs[14]

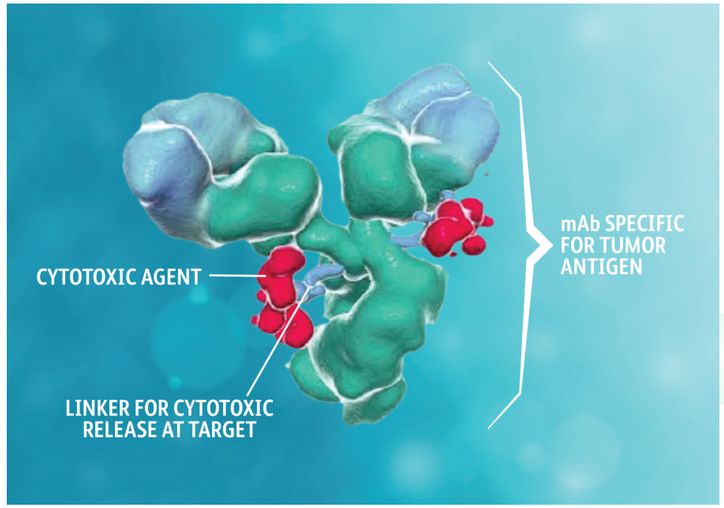
SELECT INVESTIGATIONAL PATHWAYS

CCR8 and FucGM1

ADC=antibody-drug conjugate; BsAbs=bispecific antibodies; CAR T=chimeric antigen receptor T cell; CCR8=chemokine receptor 8; CTLA-4=cytotoxic T-lymphocyte associated protein 4; Fc=fragment crystallizable; FucGM1=fucosyl-GM1; LAG-3=lymphocyte-activation gene 3; mAb=monoclonal antibody; NF=non-fucosylated; PD-1=programmed death receptor 1.

Antibody enhancements (continued)

Research suggests antibody-drug conjugates may add to the cell-killing potential of mAbs by delivering cytotoxic agents to a target site[17]

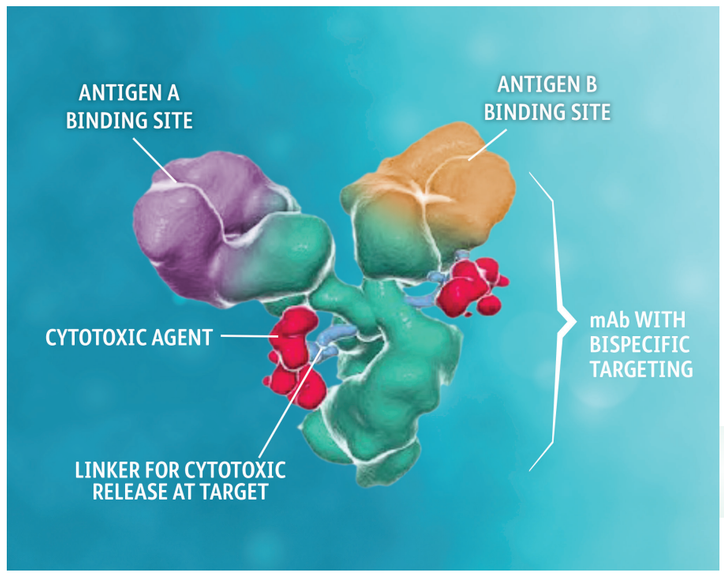


- After the ADC binds to a tumor cell, internalization occurs, the ADC linker is degraded releasing the cytotoxic agent, which may lead to cell death[17]
- Research suggests linking a mAb to a potent cytotoxic agent may potentially provide a more potent approach to tumor elimination by combining mAb and systemic therapy[17,18]

SELECT INVESTIGATIONAL PATHWAYS

CD33, EGFR, FRα, and HER3

Research suggests bispecific ADCs have unique dual-targeting characteristics that may enhance selective targeting of cancer cells[19]



- Bispecific ADCs may:
  - Reduce off-target toxicity by selectively binding to co-expressed antigens in solid tumors[19]
  - Improve internalization, which may improve delivery of cytotoxic drug[19,20]
  - Help overcome drug resistance by promoting lysosomal degradation[19]
- Bispecific ADCs may leverage unique dual-targeting technology to potentially reduce drug resistance and inhibit cancer cell proliferation and survival[19]

SELECT INVESTIGATIONAL PATHWAYS

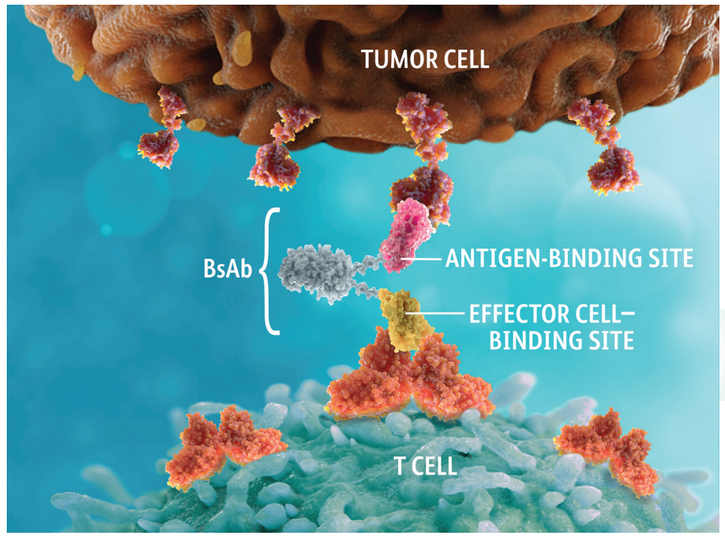
EGFR and HER3

Directed immune activity

Tumor cells can develop mechanisms to interfere with immune cell signaling, resulting in immunosuppressed tumors with no immune cell infiltration.[7]

An immunosuppressive tumor microenvironment may limit the immune response necessary to eliminate tumor cells.[7,8]

Research suggests bispecific antibodies may redirect the effector immune cells to tumor targets[21]

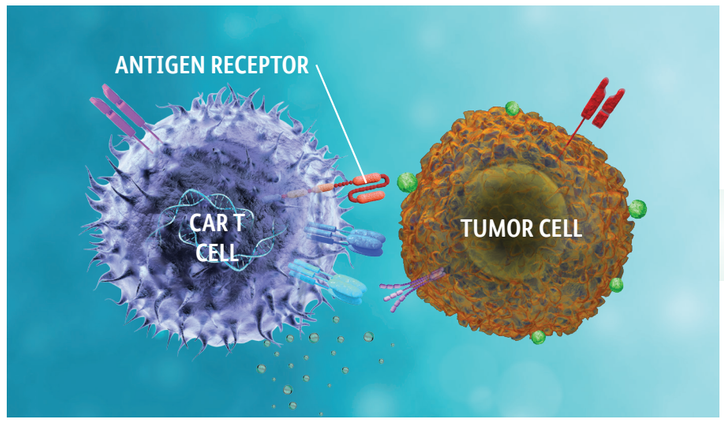


- Research suggests BsAbs may recruit immune cells to the tumor microenvironment by binding to tumor cells on one domain and immune cells on the other domain[21,22]
- Variability in the binding sites may allow for the recruitment of different immune cells (eg, by targeting CD3 for T cells or CD16 for natural killer cells)[21,22]

SELECT INVESTIGATIONAL PATHWAYS

CD33, EGFR, and HER3

Preclinical research suggests chimeric antigen receptor T cells may improve antitumor activity of T cells[23-25]



- CAR T cells are patient-derived T cells engineered to directly target tumor antigens to potentially elicit tumor cell death by enhancing cytotoxic immune cell function[23-25]

SELECT INVESTIGATIONAL PATHWAY

GPRC5D

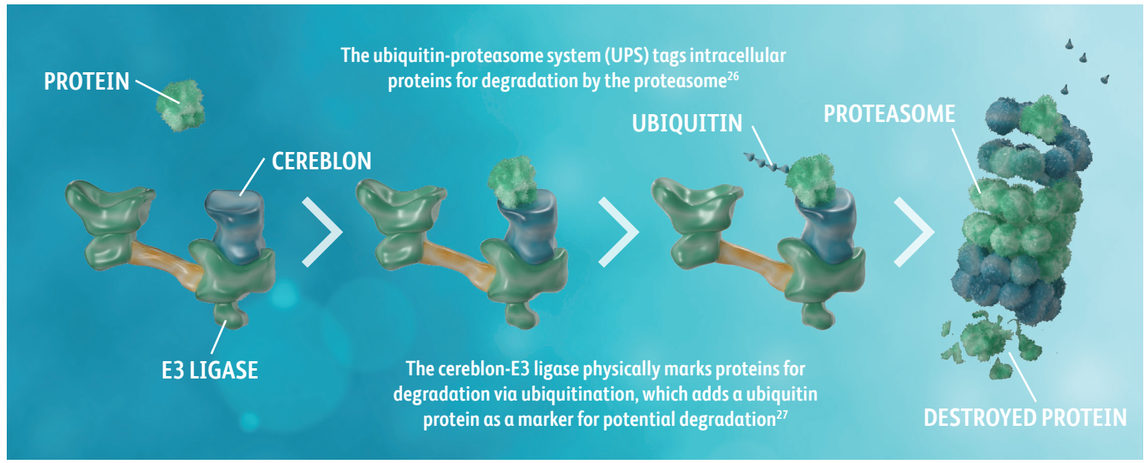
ADC=antibody-drug conjugate; BsAb=bispecific antibody; CAR T=chimeric antigen receptor T cell; CD=cluster of differentiation; EGFR=epidermal growth factor receptor; FRα=folate receptor-α; GPRC5D=G-protein coupled receptor family C group 5 member D; HER3=human epidermal growth factor receptor; mAb=monoclonal antibody.

Novel protein-targeted approaches

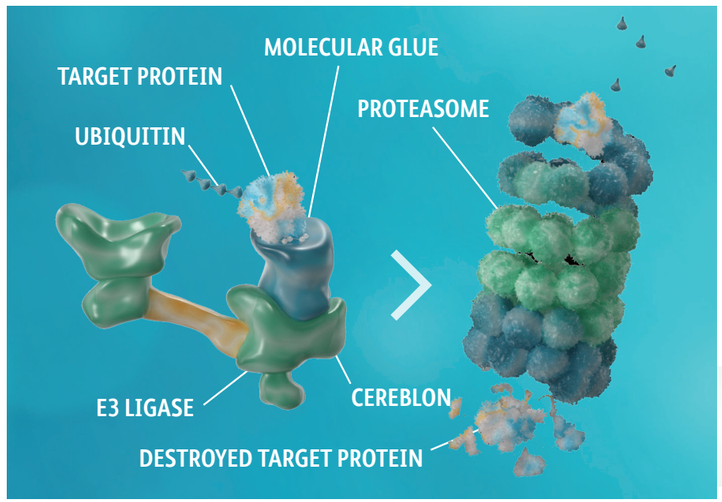
There are several key contributors to oncogenesis that are difficult to target and can cause further disease progression.[9-12]

Additionally, mutations beyond driver mutations can lead to steric hindrance, allowing RTK fusion proteins to evade inhibition and continue to drive oncogenesis.[12]

Research is exploring protein degradation pathways that may make these "undruggable" proteins more targetable by promoting their degradation through cereblon-E3 ligase complex[9]



Research suggests cereblon-modulating agents may facilitate the degradation of targeted proteins[28]

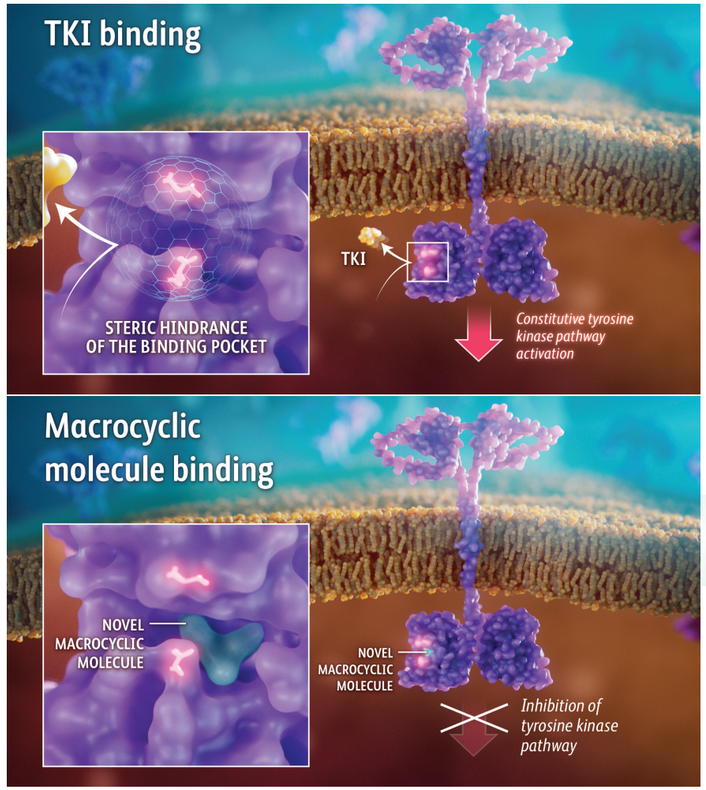


- Research suggests targeted protein degrader agents, such as cereblon-modulating agents (molecular glues) and LDDs, may induce binding of target proteins to cereblon, leading to their degradation[28,29]
- Research is exploring whether the cereblon-E3 ligase pathway can be leveraged to selectively induce the degradation of proteins involved in tumor cell growth and proliferation[9,29]

SELECT INVESTIGATIONAL PATHWAYS

Androgen receptor, Aiolos/Ikaros, Bcl-6, CD33, and CK1α

Research is exploring novel macrocyclic molecules that aim to facilitate TKI binding in the presence of conformational challenges[30-32]

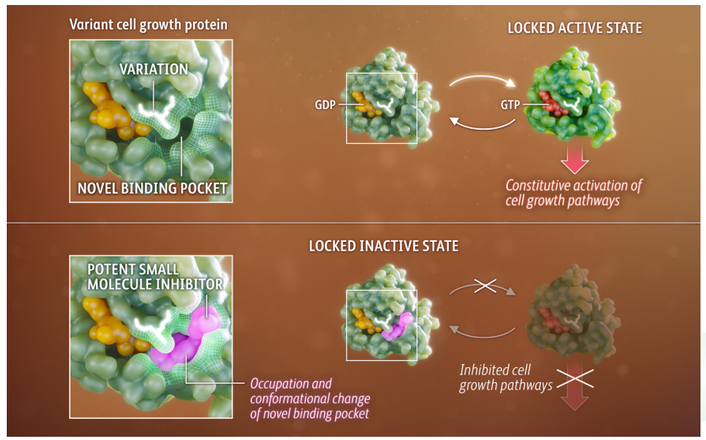


- Macrocyclic molecules are characterized by smaller size and lower molecular weight. Research suggests that these compact characteristics may allow for more precise binding and binding to the ATP pocket despite steric hindrance or other conformational challenges[30,31, 33-35]
- Overcoming steric hindrance in oncogenic fusion proteins may help prevent tumor cell growth and proliferation and lead to tumor cell death[32,35]
- Research is exploring how novel macrocyclic molecules may lead to anti-tumor activity in the presence of receptor tyrosine kinase fusion proteins[30,33,34]

SELECT INVESTIGATIONAL PATHWAYS

ROS1 and NTRK

Research suggests potent small molecules may lock some variant cell growth proteins in an inactive state[36-38]



- Research is exploring how potent small molecules can lock some variant cell growth proteins in an inactive state by occupying and causing conformational changes in novel binding pockets.[36-40]
- Potent small molecules may cause sustained inhibition of some variant cell growth proteins previously considered "undruggable," potentially leading to tumor cell death[40,41]

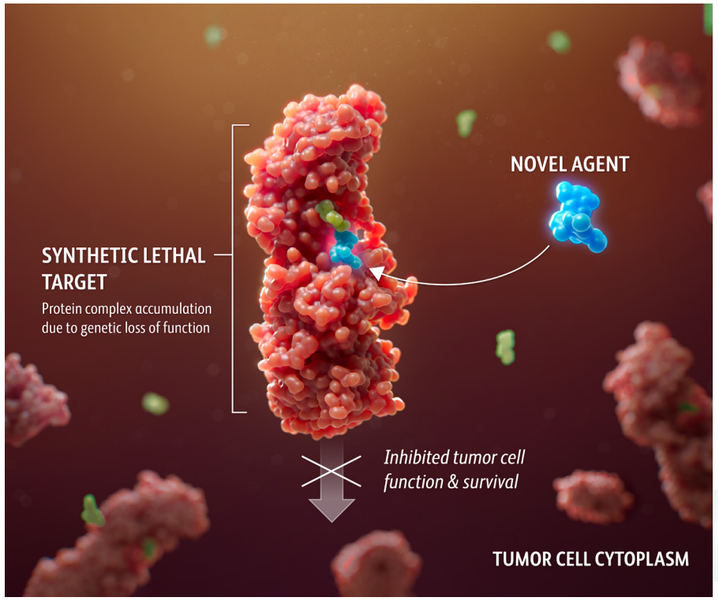
SELECT INVESTIGATIONAL PATHWAY

KRAS

ATP=adenosine triphosphate; Bcl-6=B-cell lymphoma 6; CD=cluster of differentiation; CK1α=casein kinase 1 alpha; GDP=guanosine diphosphate; GTP=guanosine triphosphate; KRAS= Kirsten rat sarcoma virus; LDD=ligand-directed degraders; NTRK=neurotrophic tyrosine receptor kinase; RTK=receptor tyrosine kinase; ROS1=proto-oncogene C-Ros1; TKI=tyrosine kinase inhibitor.

Novel protein-targeted approaches (continued)

Research suggests synthetic lethality may be used to target compensatory survival mechanisms in certain cancer cells[42-44]



- Synthetic lethality involves exploiting the deletion of two genes[45]
- Deletion of one gene by itself may not be targetable; however, the deletion of the second gene may lead to compensatory survival mechanisms, such as the accumulation of protein complexes. These protein complexes may present an opportunity for inhibition and ultimately, cancer cell death[44,45]
- Synthetic lethality may allow for more precise therapies, potentially improving safety and treatment outcomes by inhibiting tumor cell proliferation and survival while sparing normal cells[43]

SELECT INVESTIGATIONAL PATHWAY

PRMT5

BMS continues to explore optimizing current strategies and pathways, and to investigate novel targets and approaches

PRMT5= protein arginine methyltransferase 5.

BMS remains committed to investigating the potential of innovative approaches to anticancer strategies and pathways

For more information, please visit
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