Dostarlimab

as a miracle drug: rising hope against cancer treatment

ABOUT

COLORECTAL CANCER

PD1/PDL1 SIGNALING

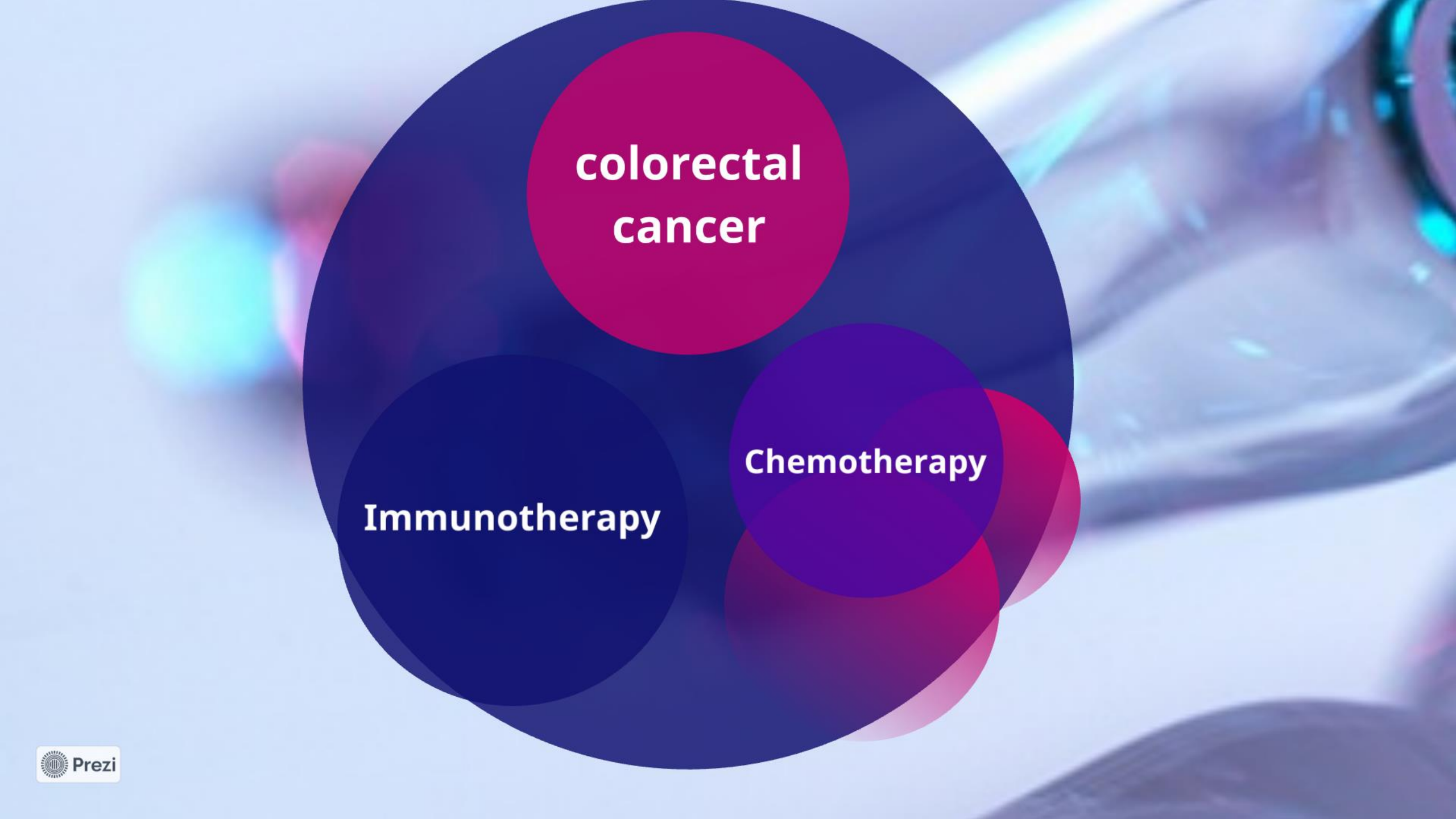
IMMUNOTHERAPY

CHEMOTHERAPY

DOSTARLIMAB MECHANISM OF ACTION

TIMELINE

References



How does colorectal cancer start?

Most colorectal cancers start as a growth on the inner lining of the colon or rectum. These growths are called polyps.
Some types of polyps can change into cancer over time (usually many years), but not all polyps become cancer. The chance of a polyp turning into cancer depends on the type of polyp it is.
There are different types of polyps.

- Adenomatous polyps (adenomas)
- Hyperplastic polyps and inflammatory polyps
- Sessile serrated polyps (SSP) and traditional serrated adenomas (TSA)

The stage (extent of spread) of a colorectal cancer depends on how deeply it grows into the wall

Types

Cause

Treatment

Survival rates

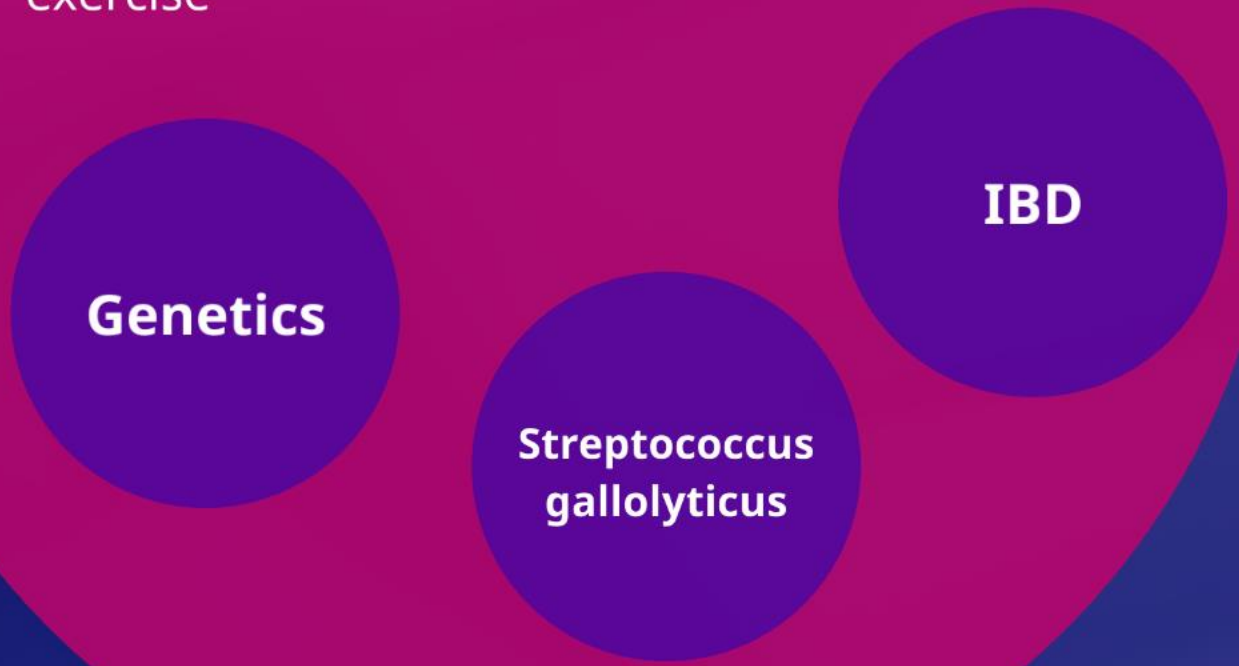
Types of cancer in the colon and rectum

Most colorectal cancers are adenocarcinomas
These cancers start in cells that make mucus to lubricate the inside of the colon and rectum.

- Carcinoid tumors
- Gastrointestinal stromal tumors (GISTs)
- Lymphomas
- Sarcomas

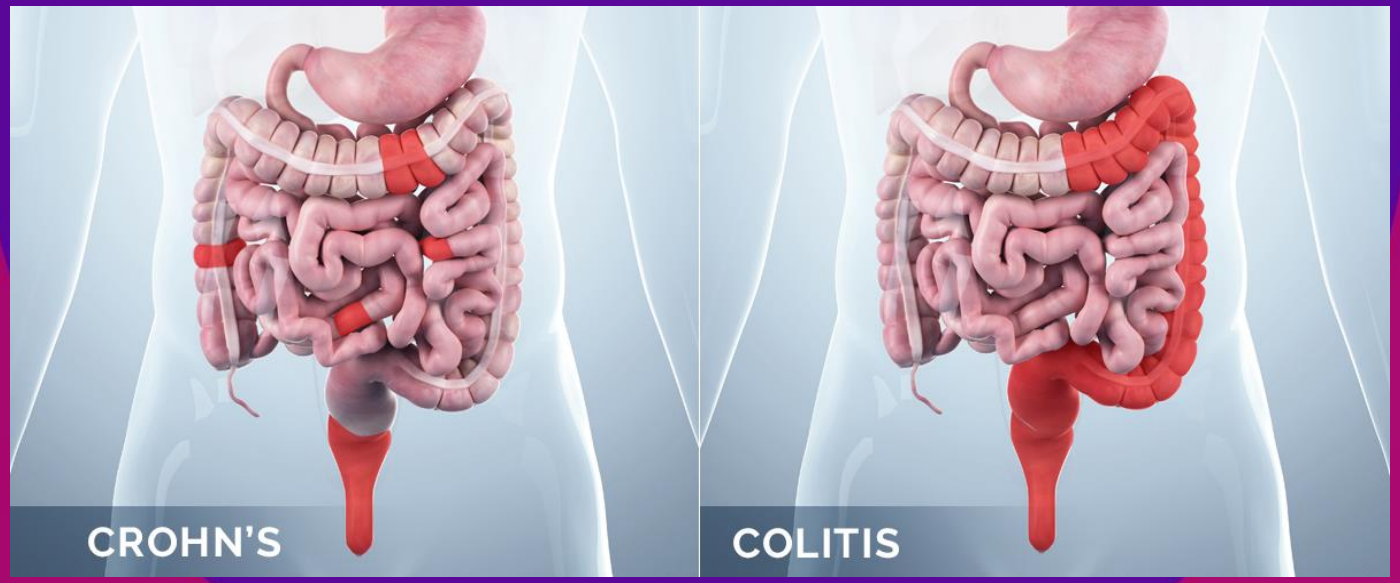
Causes:

75–95% of colorectal cancer cases occur in people with little or no genetic risk
Risk factors include older age, male sex,high intake of fat, sugar, alcohol, red meat, processed meats, obesity, smoking, and a lack of physical exercise



Inflammatory bowel disease

People with inflammatory bowel disease (ulcerative colitis and Crohn's disease) are at increased risk of colon cancer



Genetics

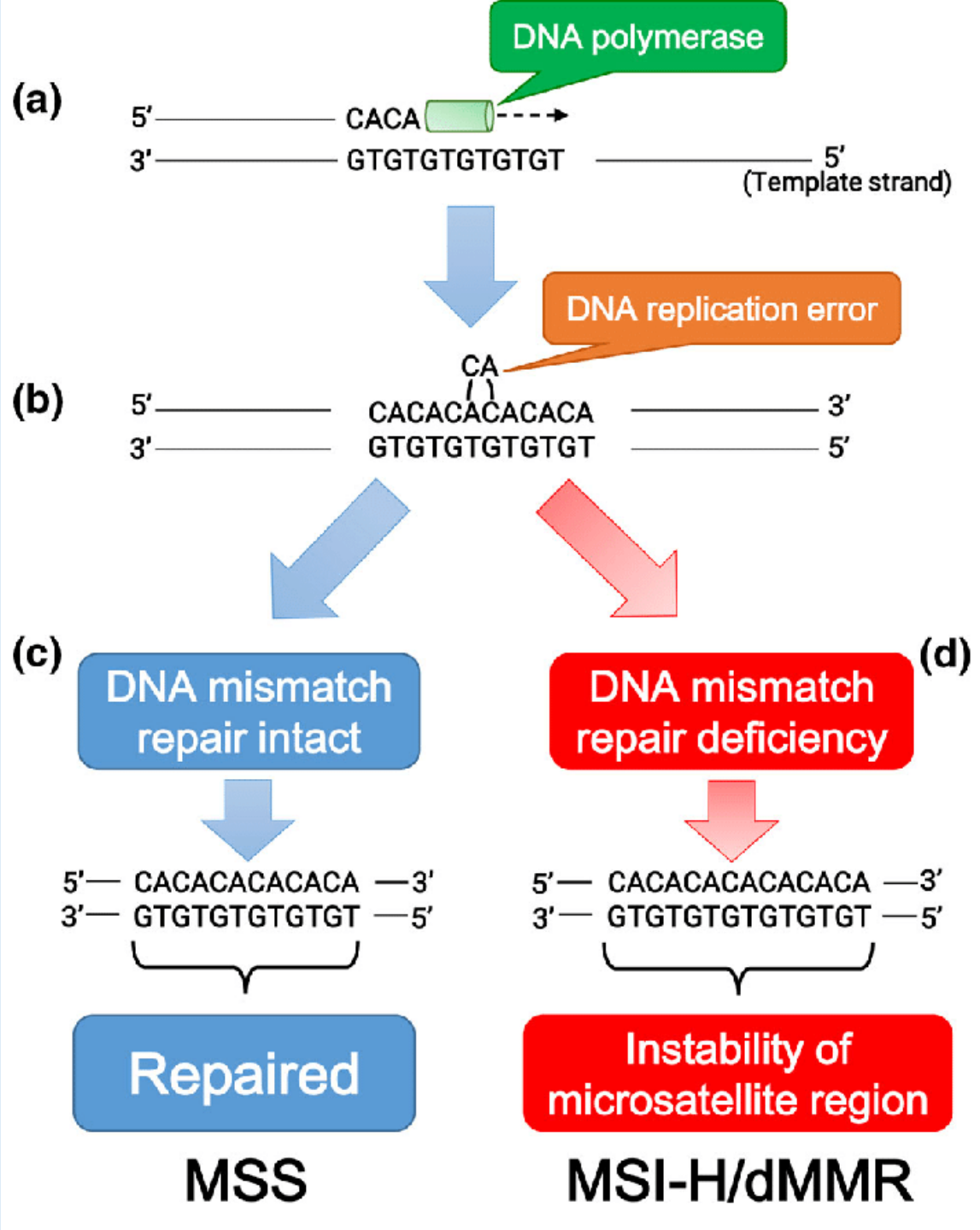
Those with a family history in two or more first-degree relatives (such as a parent or sibling) have a two to threefold greater risk of disease
A number of genetic syndromes are also associated with higher rates of colorectal cancer. The most common of these is hereditary nonpolyposis colorectal cancer (HNPCC, or Lynch syndrome) which is present in about 3% of people with colorectal cancer.

dMMR

dMMR

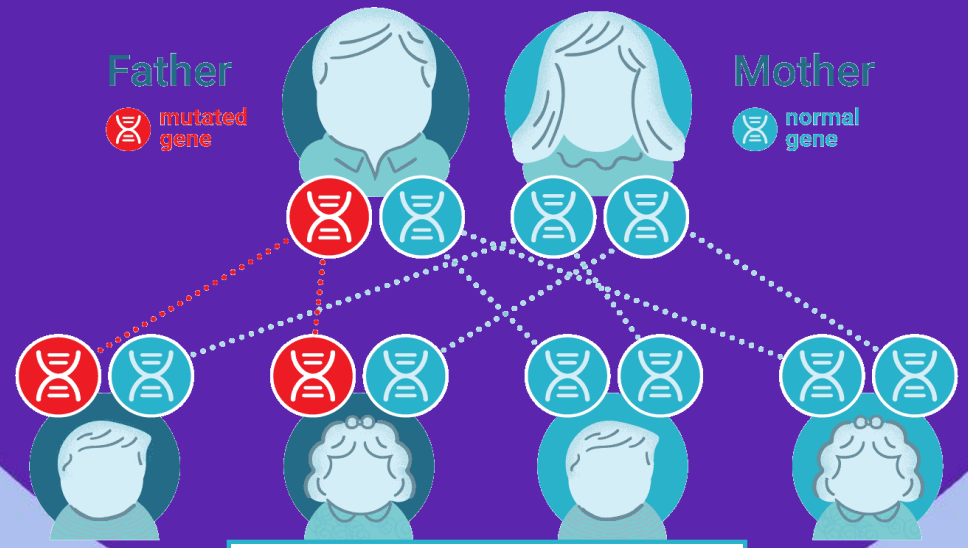
A change that occurs in certain cells (such as cancer cells),Deficient mismatch repair (dMMR) and its characteristic genetic signature, high levels of microsatellite instability (MSI-H)
cancers are characterized by a high tumor mutational load and potential responsiveness to anti-programmed cell death 1 (PD-1)-based

Lynch syndrome

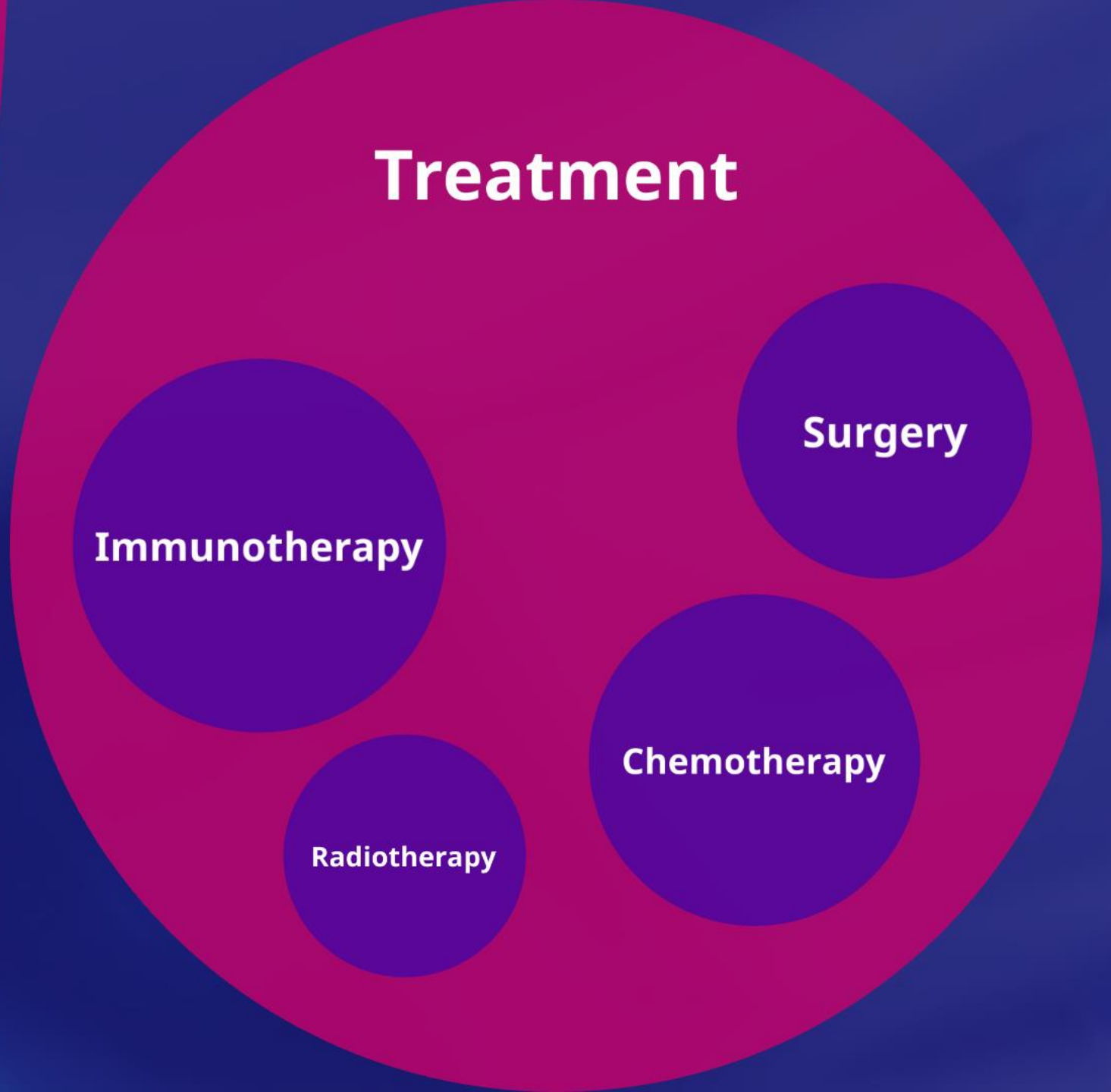

DNA polymerase
(a)
5′
CACA
3′
GTGTGTGTGTGT
5′
(Template strand)
DNA replication error
CA
(b)
5′
CACACACACACA
3′
3′
GTGTGTGTGTGT
5′
(c)
DNA mismatch repair intact
(d)
DNA mismatch repair deficiency
5′— CACACACACACA —3′
3′— GTGTGTGTGTGT —5′
5′— CACACACACACACA —3′
3′— GTGTGTGTGTGTGT —5′
Repaired
Instability of microsatellite region
MSS
MSI-H/dMMR

Genetics and Lynch syndrome

Lynch syndrome is due to inherited changes (mutations) in genes that affect DNA mismatch repair, a process that fixes mistakes made when DNA is copied. These genes (MLHL, MSH2, MSH6, PMS2, and EPCAM) normally protect you from getting certain cancers, but some mutations in these genes prevent them from working properly.

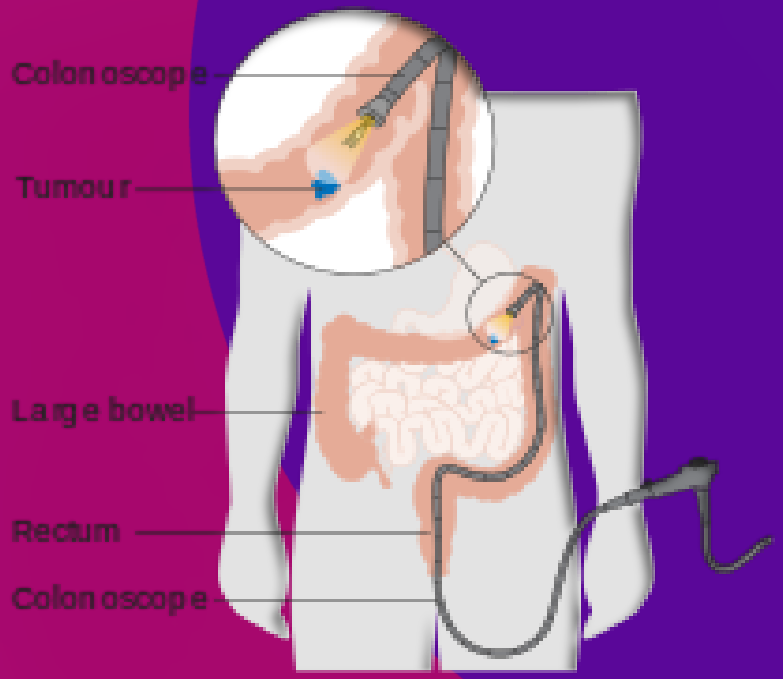


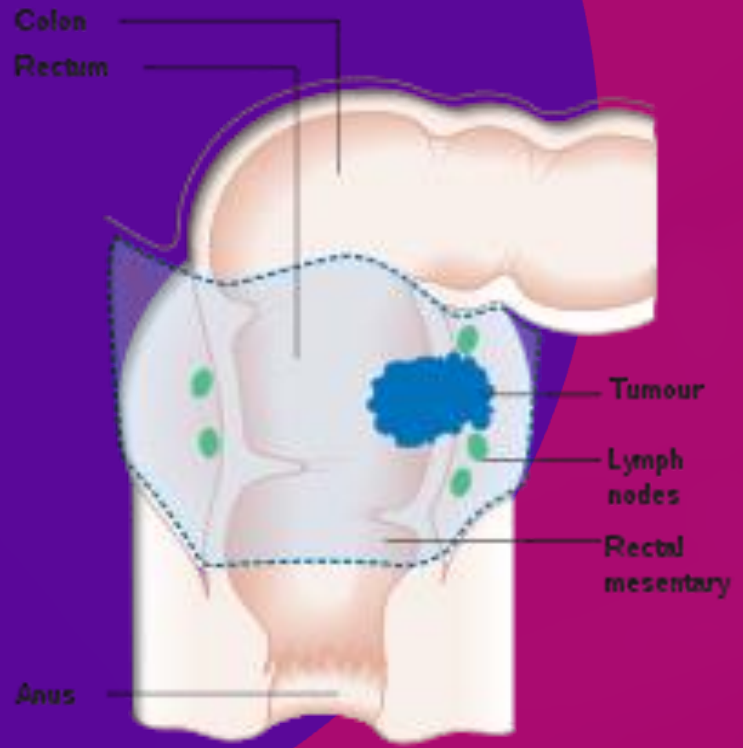
50% chance of each child inheriting the mutated gene


Treatment
Surgery
Immunotherapy
Chemotherapy
Radiotherapy

Surgery

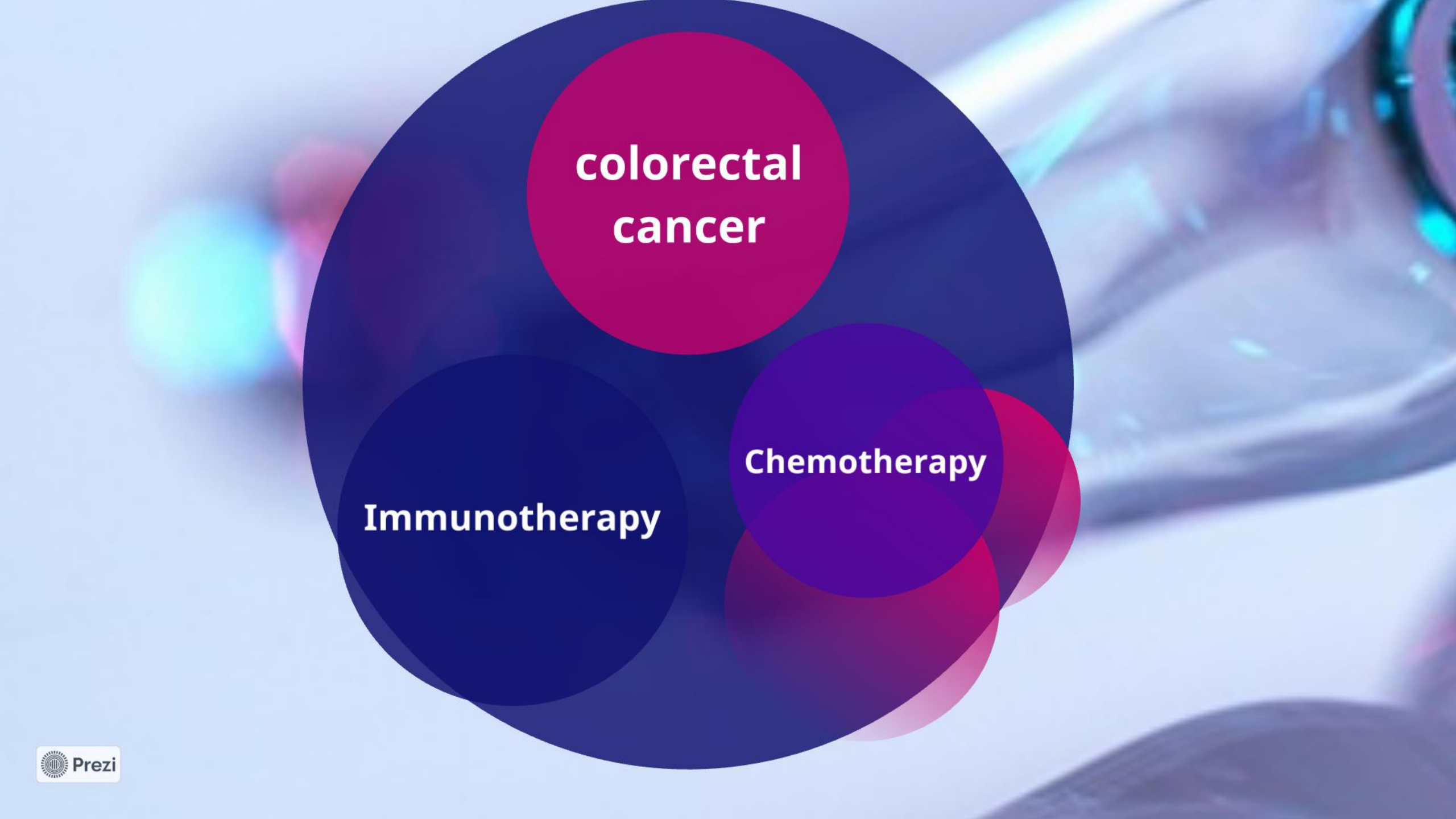
At an early stage, colorectal cancer may be removed during a colonoscopy





Survival rate

the five-year survival rate for colorectal cancer is less than 60%. In the developed world about a third of people who get the disease die from it



Types of Chemotherapy:

Alkylating agents.
Antimetabolites.
Anti-tumor antibiotics.
Topoisomerase inhibitors.
Mitotic inhibitors.
Plant alkaloids.

platinum-based chemotherapy

side effect grades

Side effect grades

1

Transient (goes away after a short time) or mild discomfort; no limitation in activity; no medical intervention/therapy required.

2

Your daily activity is affected mild to moderately – some assistance might be needed; no or minimal medical intervention/therapy required.

3

Your daily activity is markedly reduced – some assistance usually required; medical intervention/therapy required, hospitalisation or hospice care possible.

4

Extreme limitation to daily activity, significant assistance required

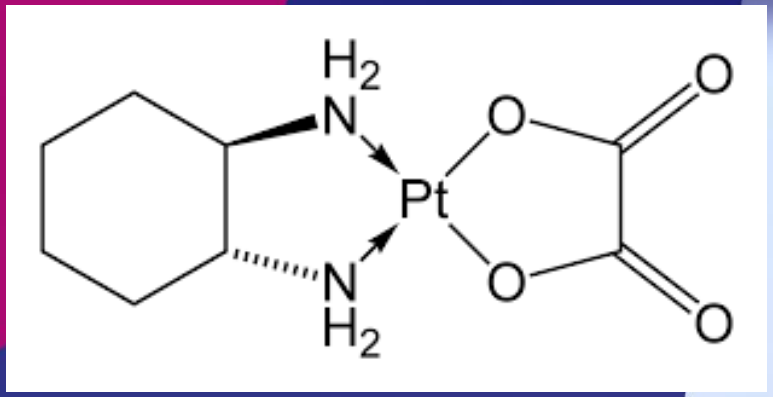
Chemotherapy in CRC

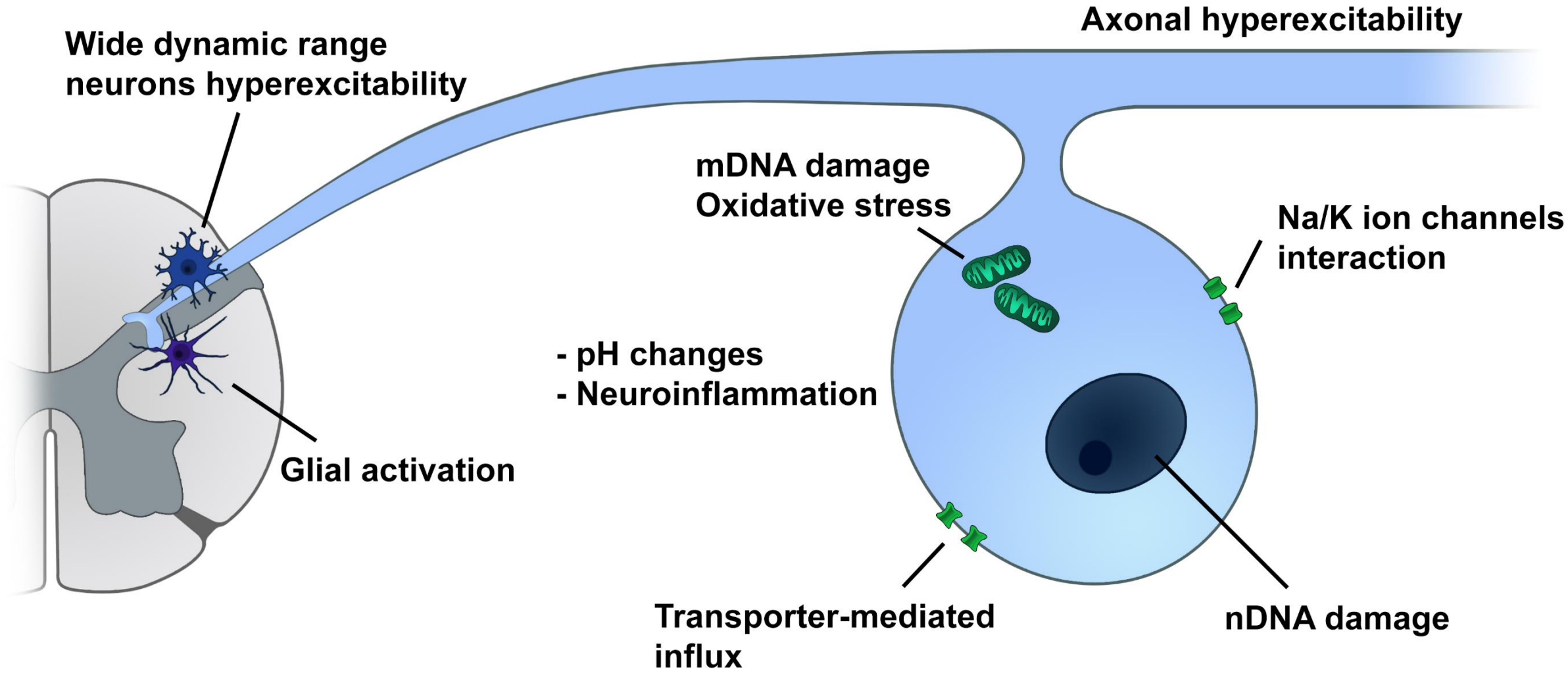
In Stage I colon cancer, no chemotherapy is offered, and surgery is the definitive treatment. The role of chemotherapy in Stage II colon cancer is debatable
It is also known that the people who carry abnormalities of the mismatch repair genes do not benefit from chemotherapy
For stage III and Stage IV colon cancer, chemotherapy is an integral part of treatmen
agents fluorouracil, capecitabine or oxaliplatin increases life expectancy. If the lymph nodes do not contain cancer
. If the cancer is widely metastatic or unresectable, treatment is then palliative.

Platinum-based chemotherapy

*Platinum-based drugs cisplatin, carboplatin, and oxaliplatin are widely used for chemotherapeutic eradication of cancer.
*causing damage to the DNA of cancer cells to prevent them from multiplying.
*Oxaliplatin, the First Platinum-Based Compound Approved for Colorectal Cancer Treatmen

Oxaliplatin is considered the most neurotoxic chemotherapy




Wide dynamic range
neurons hyperexcitability
Axonal hyperexcitability
mDNA damage
Oxidative stress
Na/K ion channels
interaction
- pH changes
- Neuroinflammation
Glial activation
Transporter-mediated
influx
nDNA damage

Immunotherapy

.Cancer immunotherapy aims to re-activate the immune system, which
has been suppressed by tumor cells in numerous ways
.their potential of reaching the smallest of tumors where surgeons might not.
.Another brilliant insight in cancer immunotherapy was by the Nobelprize-winning discovery of T-cell checkpoints such as CTLA-4 and PD1

The different types of immunotherapy include:

- Monoclonal antibodies and immune checkpoint inhibitors
- Non-specific immunotherapies
- Oncolytic virus therapy
- T-cell therapy
- Cancer vaccines

Monoclonal Antibody-Based Cancer Immunotherapy

mAB-based immunotherapy

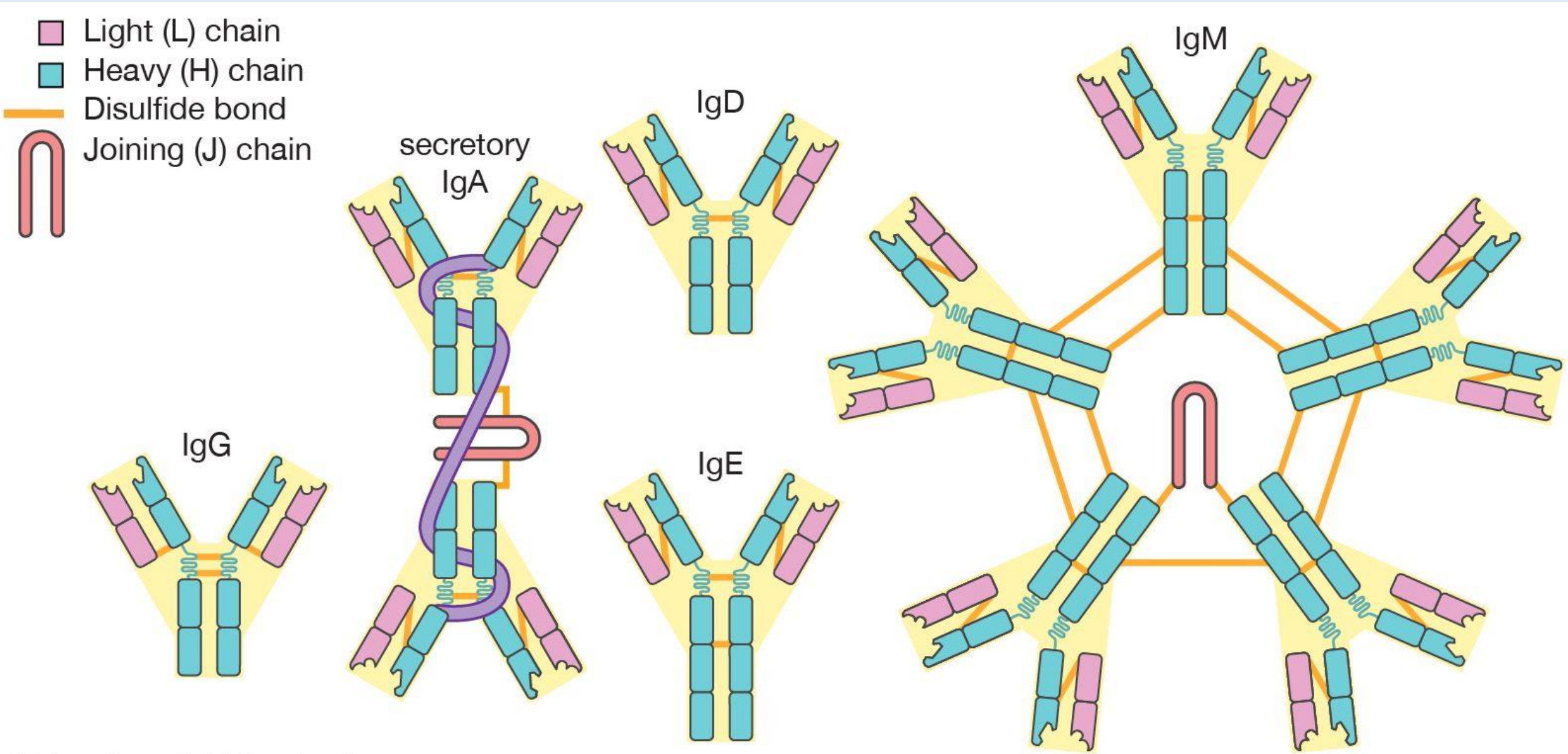
When the immune system detects something harmful, it makes antibodies. Antibodies are proteins that fight infection by attaching to antigens. Antigens are molecules that start the immune response in your body

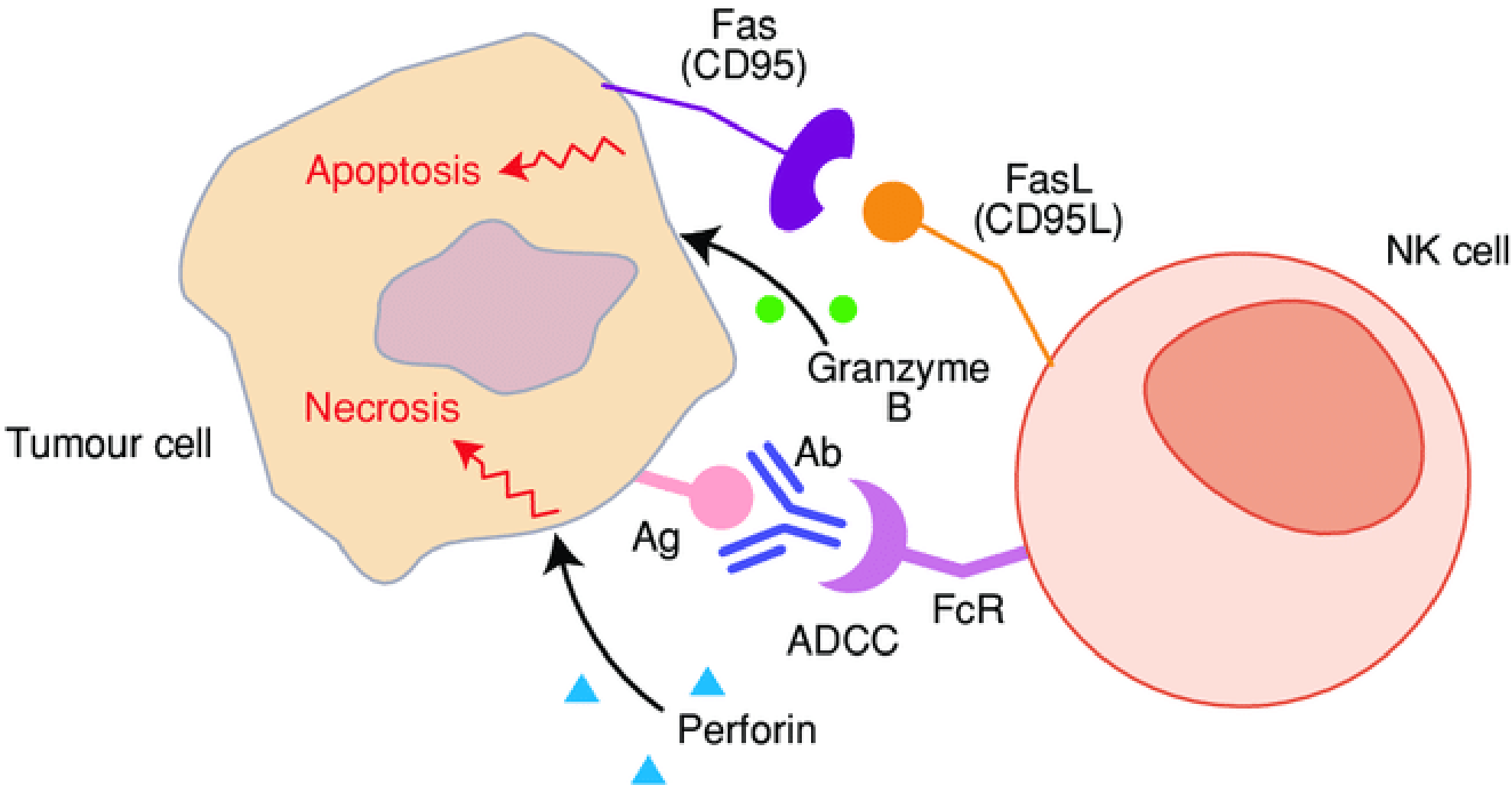
Types

There are five different types of immunoglobins based on the type of heavy chains. These include IgA, IgD, IgE, IgG, and IgM.

The most common form of immunoglobulin used for antibody-based immunotherapy is **IgG**.

attributed to its interaction with **FcR** and **FcγR**, which are largely found in natural killer cells, macrophages, monocytes and granulocytes such as eosinophils or basophils.





The natural killer (NK)-cell response to tumour cells

Types of mAB immunotherapy

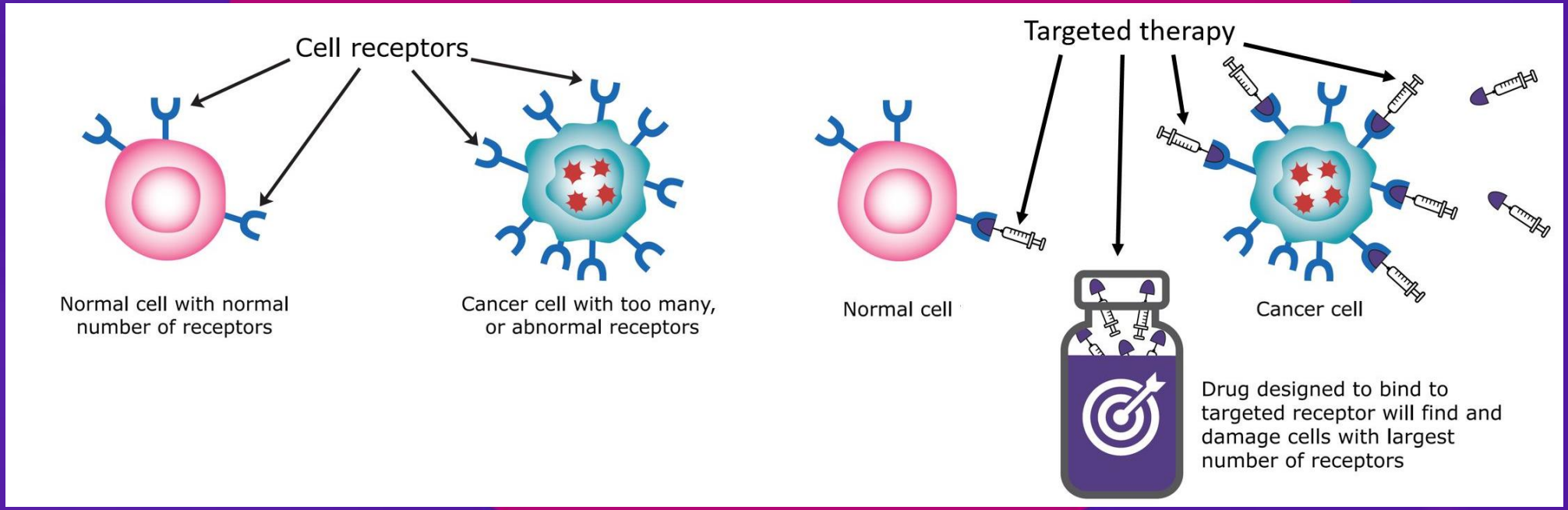
Immune checkpoint inhibitors

Target therapy

Target therapy

to block the activity of abnormal proteins in cancer cells

a cancer treatment using medication that targets a cancer's specific genes, proteins, or the tissue environment that helps the tumor grow and survive.



Immune checkpoint inhibitors

boost your immune system by inhibiting or stopping immune checkpoints. Immune checkpoints are used by the body to naturally stop an immune system response and prevent the immune system from attacking healthy cells

Dostarlimab

PD1/PDL1 Signaling

Immunotherapy for CRC

Immunotherapy with immune checkpoint inhibitors has been found to be useful for a type of colorectal cancer with mismatch repair deficiency and microsatellite instability.**Pembrolizumab** is approved for advanced CRC tumours that are MMR deficient and have failed usual treatments.

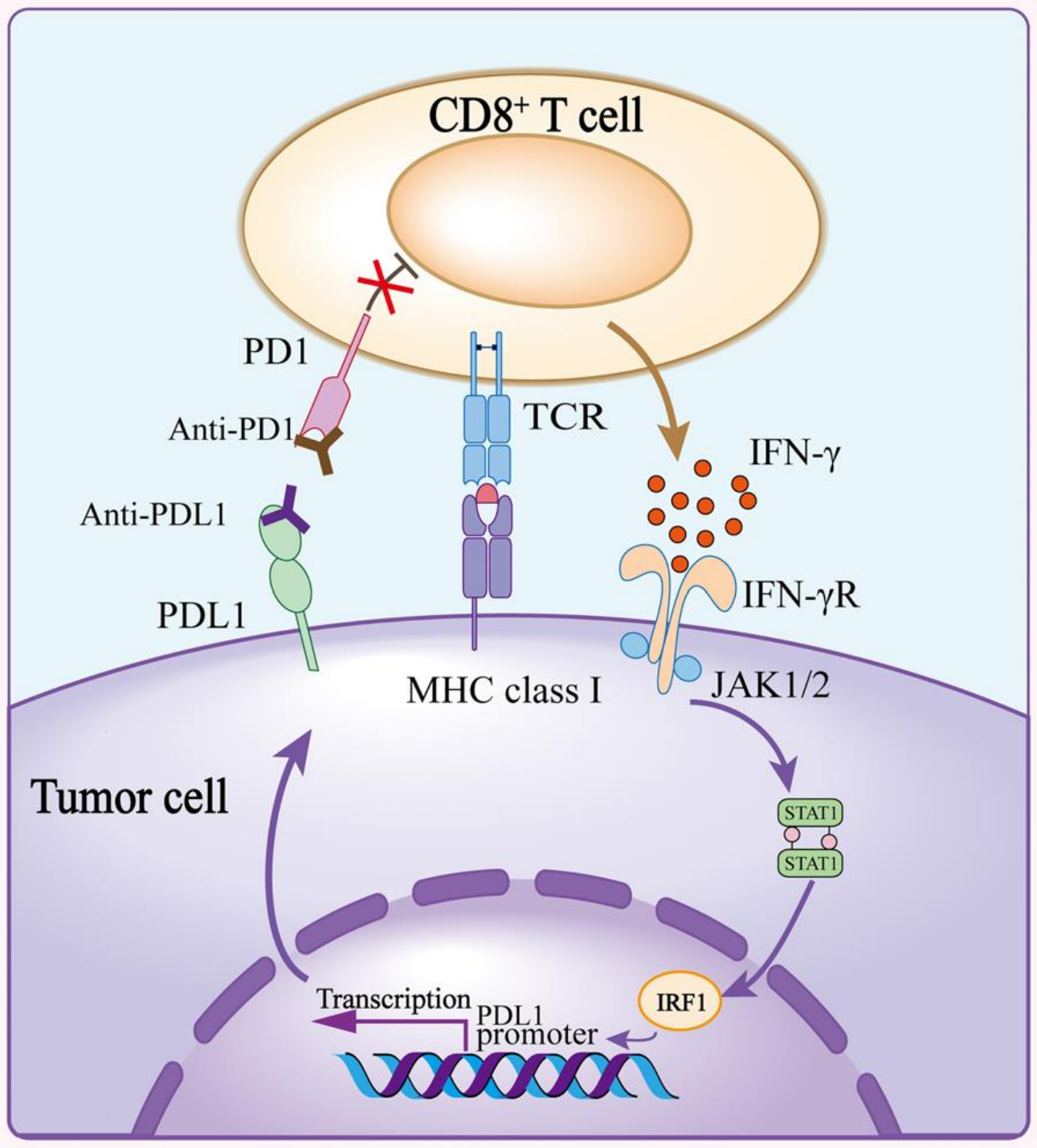
in a prospective phase 2 study published in June 2022 in, 12 patients with Deficient Mismatch Repair (dMMR) stage II or III rectal adenocarcinoma were administered single-agent **dostarlimab**

every three weeks for six months. After a median follow-up of 12 months , all 12 patients had a complete clinical response with no evidence of tumor on MR

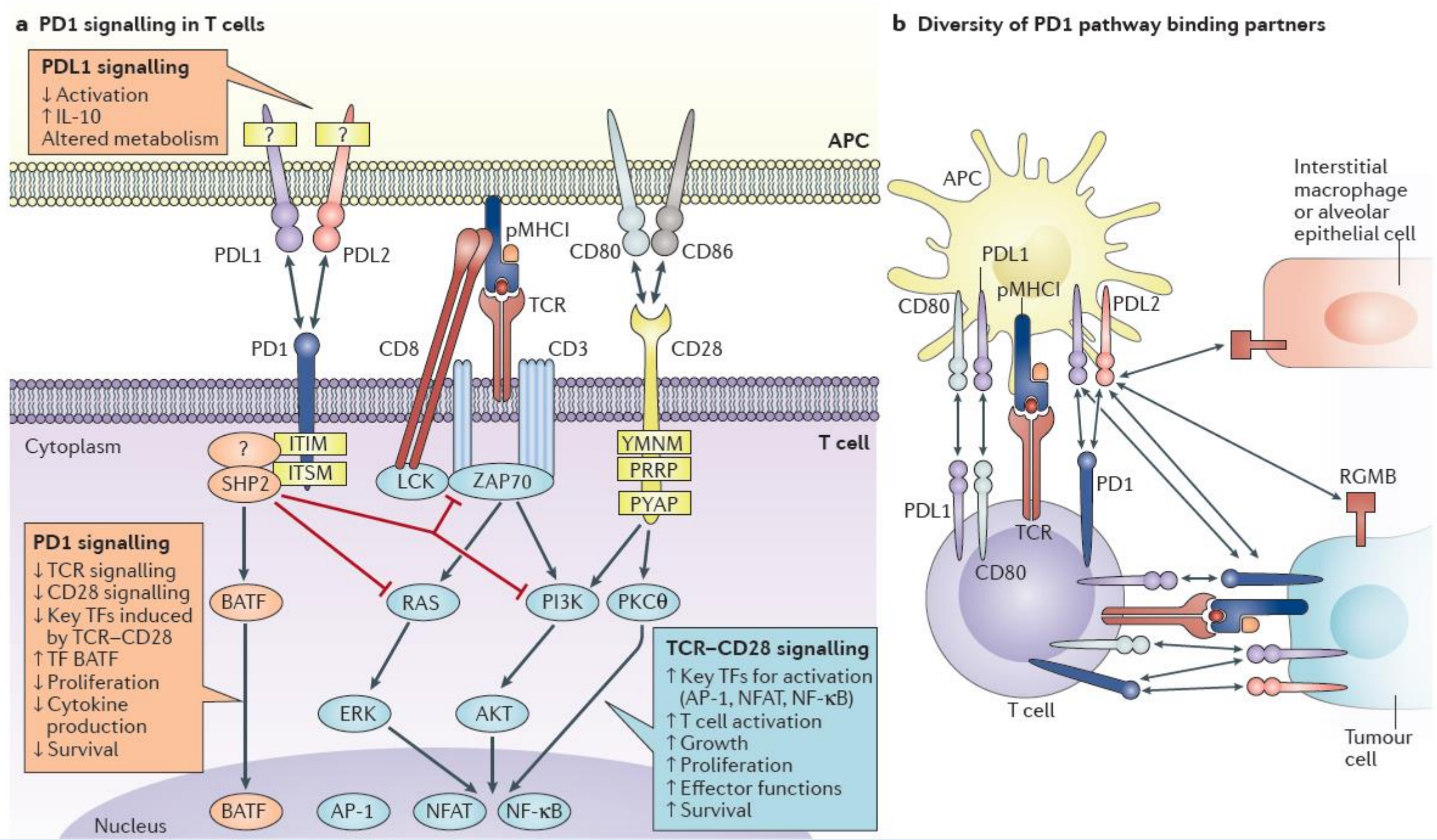
PD1 signalling in T cells

PRIMARY RESISTANCE

PD1/PDL1 checkpoint Signaling


CD8+ T cell
PD1
Anti-PD1
Anti-PDL1
PDL1
TCR
IFN-γ
IFN-γR
MHC class I
JAK1/2
Tumor cell
STAT1
STAT1
IRF1
Transcription
PDL1
promoter

PD1 signaling T Cells


a PD1 signalling in T cells
PDL1 signalling
↓ Activation
↑ IL-10
Altered metabolism
APC
?
?
PDL1
PDL2
pMHCI
CD80
CD86
TCR
PD1
CD8
CD3
CD28
Cytoplasm
T cell
?
ITIM
ITSM
SHP2
LCK
ZAP70
YMNM
PRRP
PYAP
PD1 signalling
↓ TCR signalling
↓ CD28 signalling
↓ Key TFs induced by TCR–CD28
↑ TF BATF
↓ Proliferation
↓ Cytokine production
↓ Survival
BATF
RAS
PI3K
PKCθ
ERK
AKT
TCR–CD28 signalling
↑ Key TFs for activation (AP-1, NFAT, NF-κB)
↑ T cell activation
↑ Growth
↑ Proliferation
↑ Effector functions
↑ Survival
BATF
AP-1
NFAT
NF-κB
Nucleus
b Diversity of PD1 pathway binding partners
APC
PDL1
pMHCI
CD80
PDL2
Interstitial macrophage or alveolar epithelial cell
RGMB
PD1
PDL1
TCR
CD80
T cell
Tumour cell

PD1 signalling in T cells

PRIMARY RESISTANCE

PD1/PDL1 checkpoint Signaling

Primary resistance

in anti- PD1/PDL1 therapy, tumors can escape tumor rejection by shaping a hostile tumor microenvironment (TME) to impede the antitumor efficacy of T cells. This may occur due to insufficient antigen immunogenicity, disfunction of antigen presentation, irreversible T cell exhaustion, resistance of IFN-g signaling, and immunosuppressive TME

Classic Oncogene Mutation

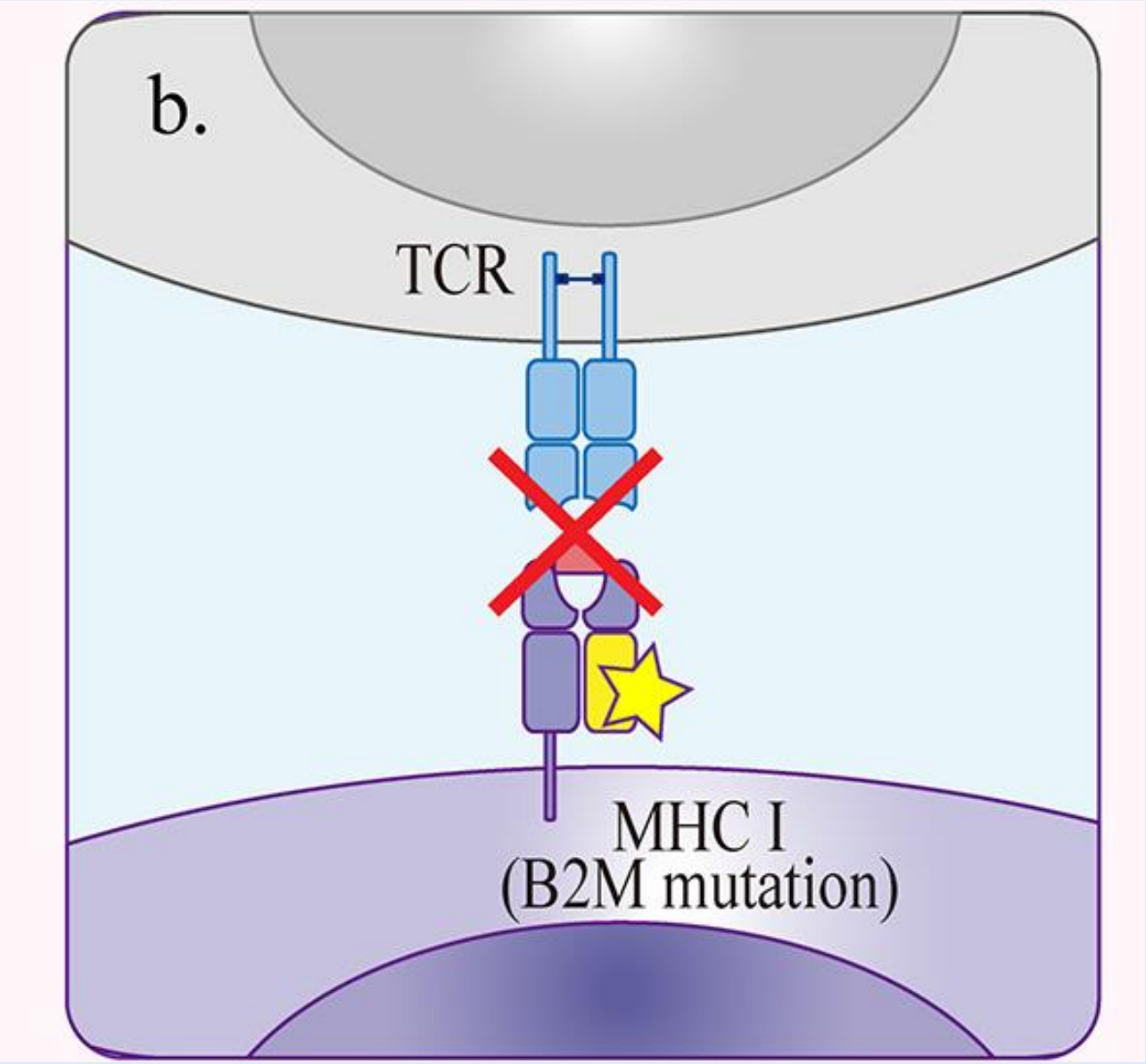
Immunosuppressive Microenvironment

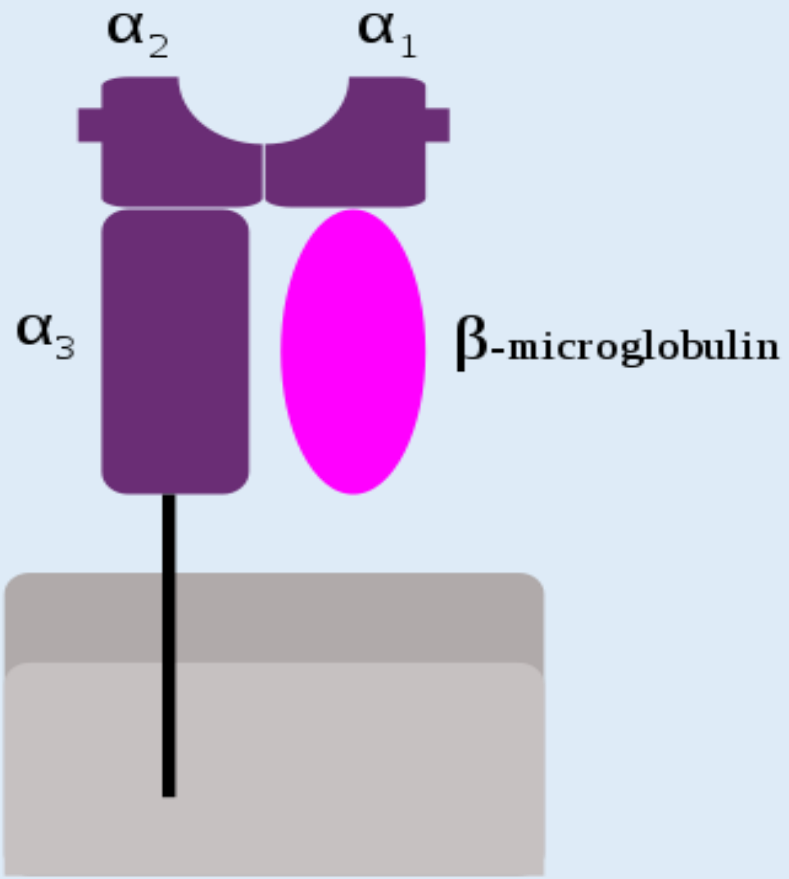
Resistance of IFN-g Signaling

Irreversible T Cell Exhaustion

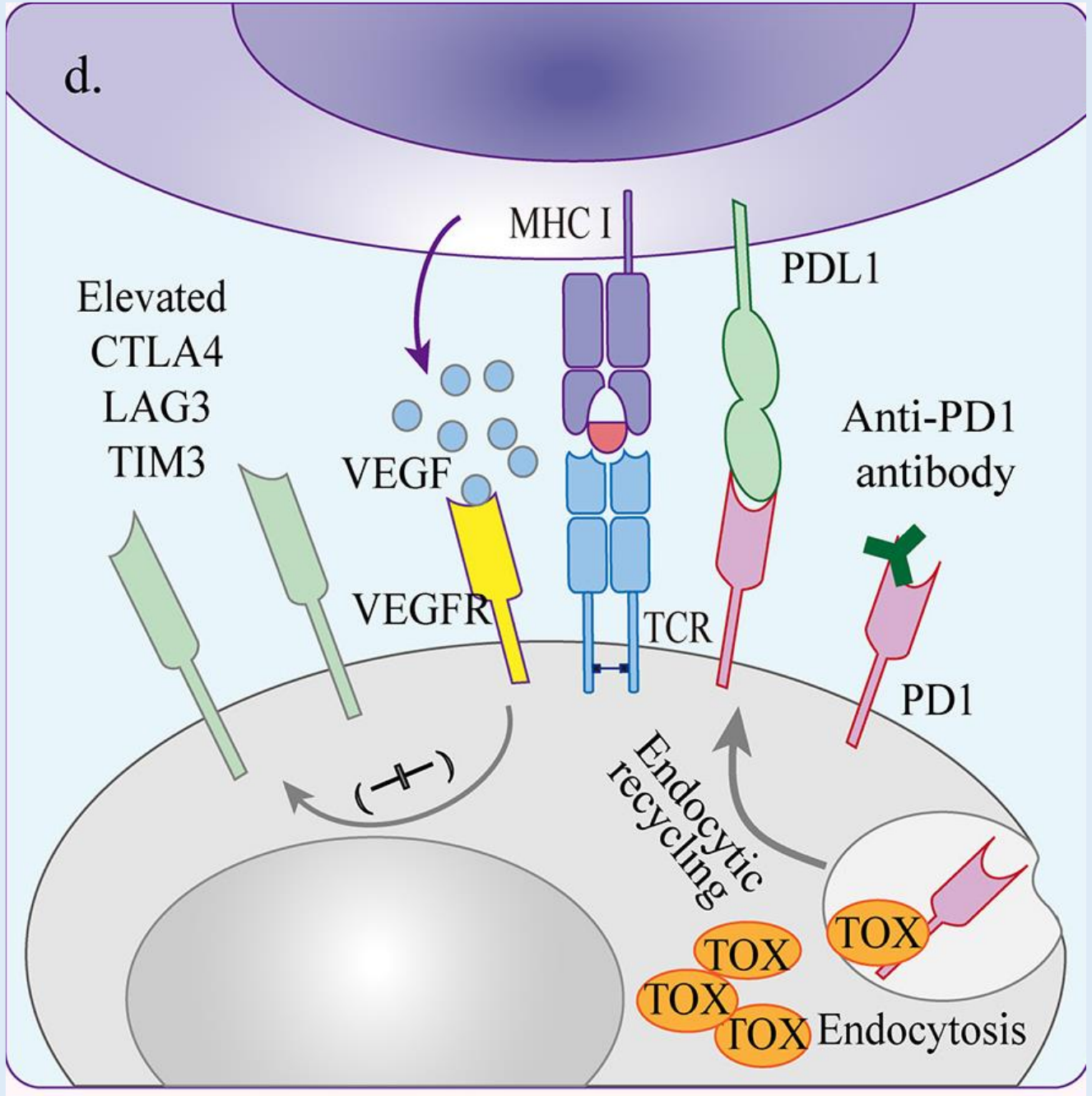
Disfunction of MHCs

Disfunction of MHCs

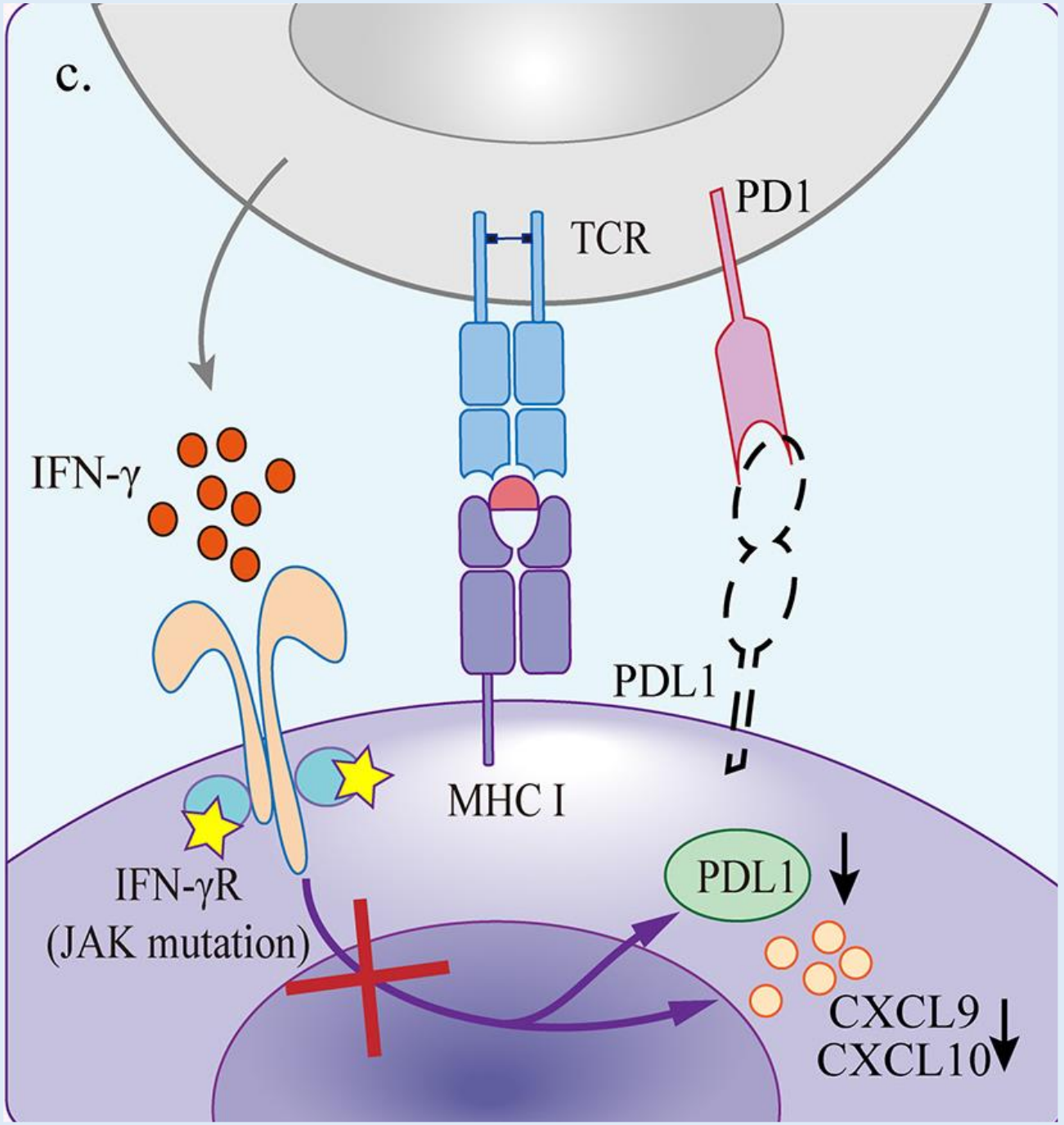

b.
TCR
MHC I
(B2M mutation)


α2
α1
α3
β-microglobulin

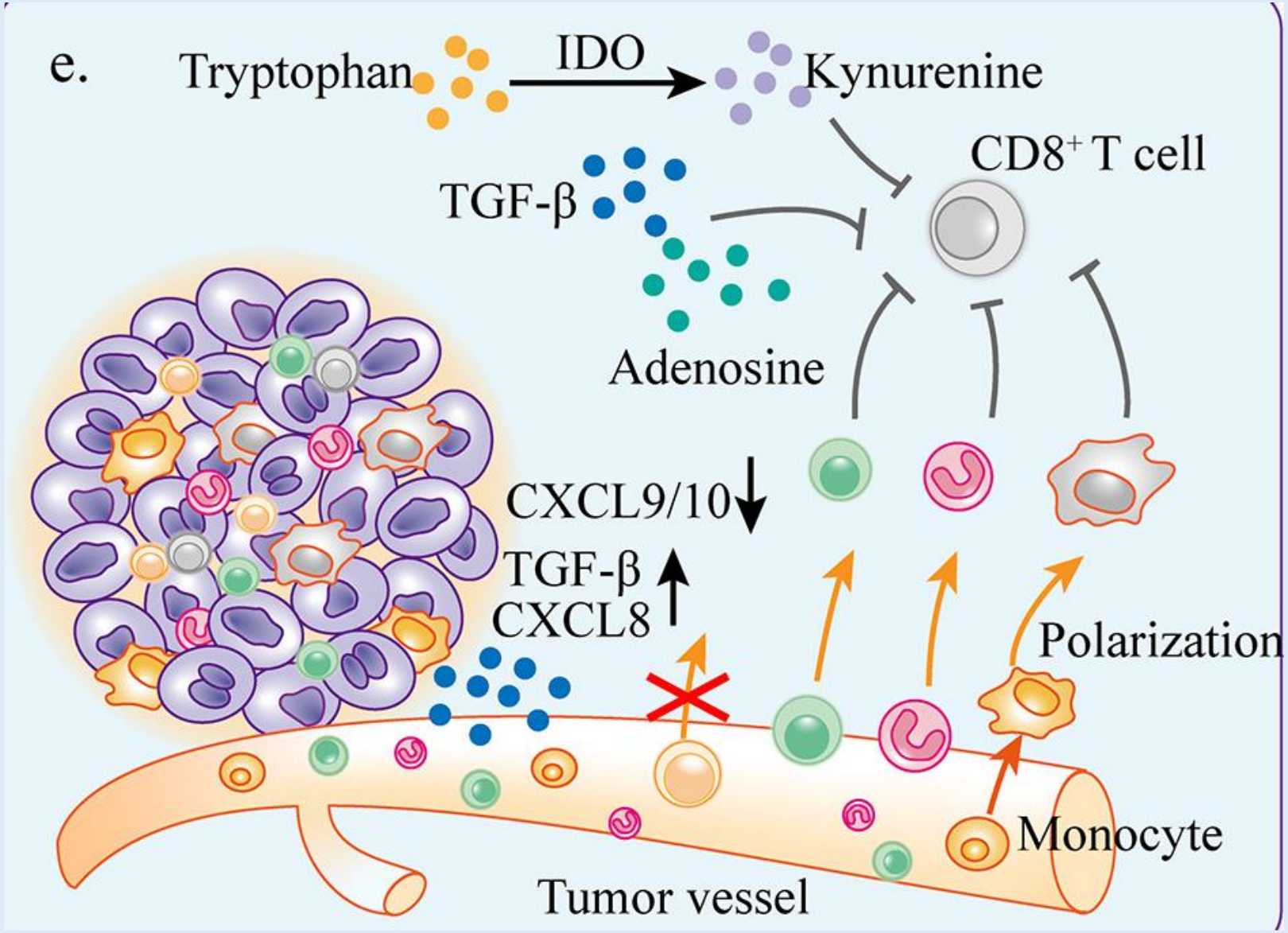
Irreversible T Cell Exhaustion


d.
MHC I
PDL1
Elevated
CTLA4
LAG3
TIM3
VEGF
Anti-PD1
antibody
VEGFR
TCR
PD1
Endocytic
recycling
TOX
TOX
TOX
TOX
Endocytosis

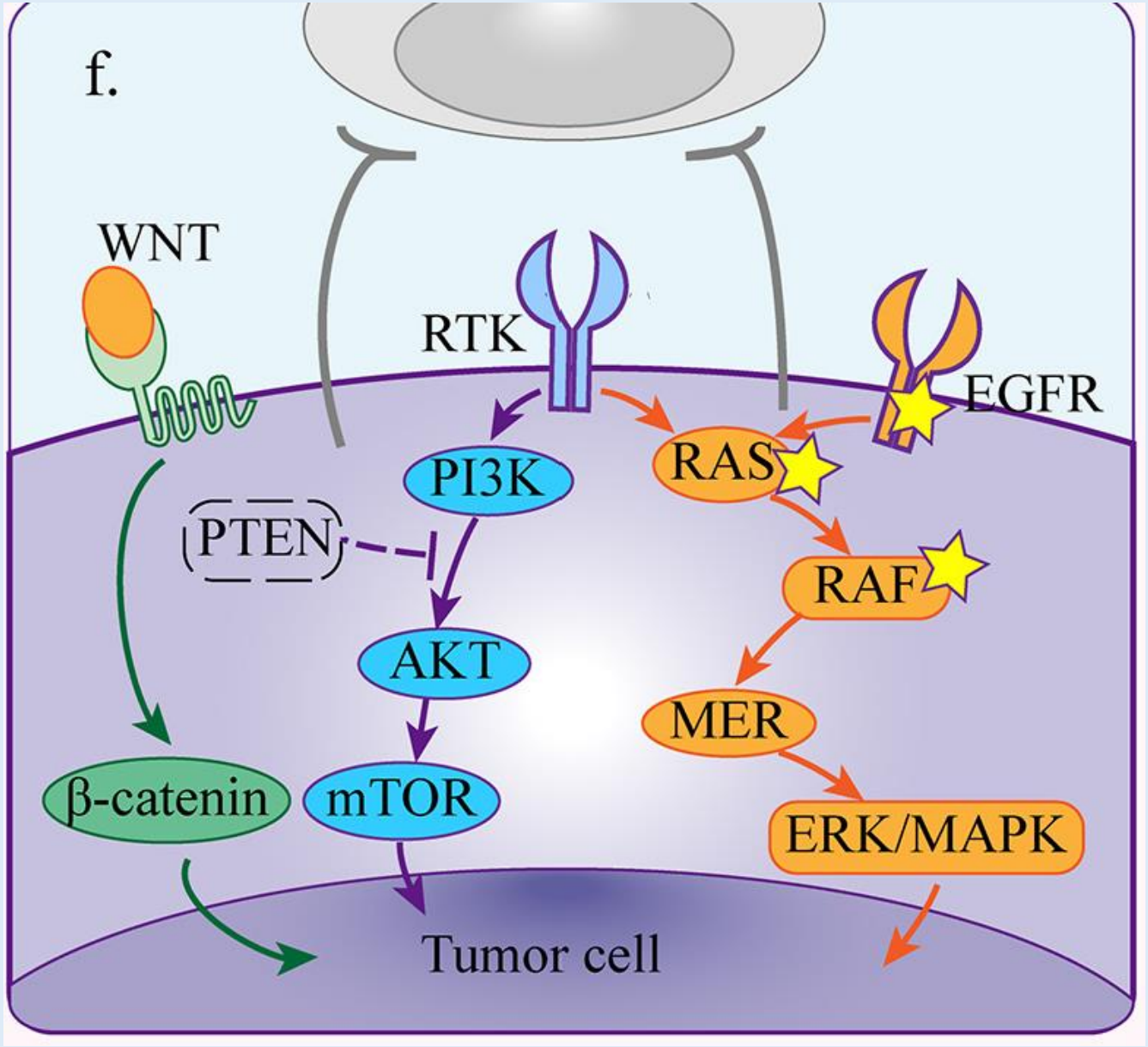
Resistance of IFN-g Signaling

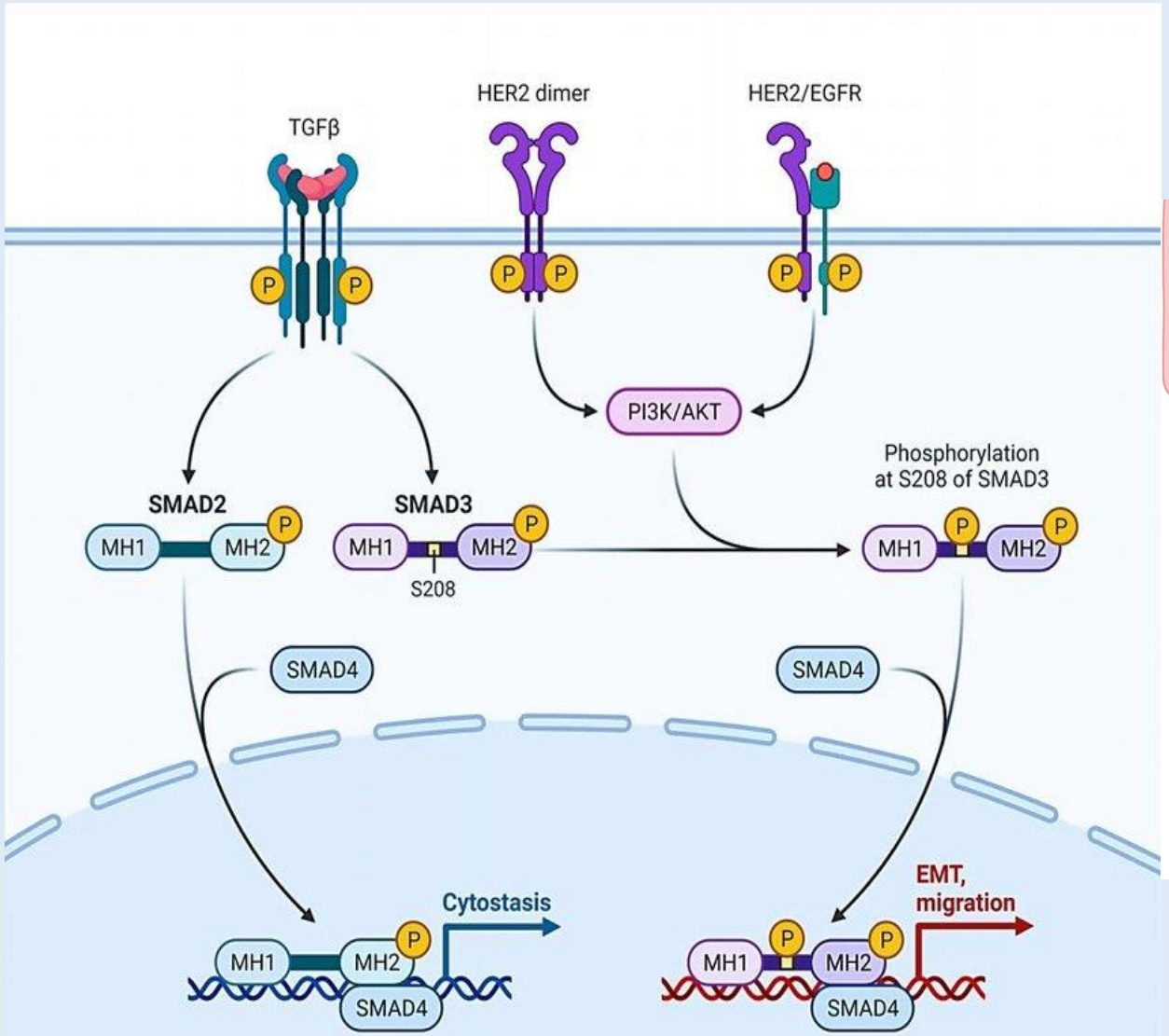

c.
PD1
TCR
IFN-γ
PDL1
MHC I
IFN-γR
(JAK mutation)
PDL1
CXCL9
CXCL10

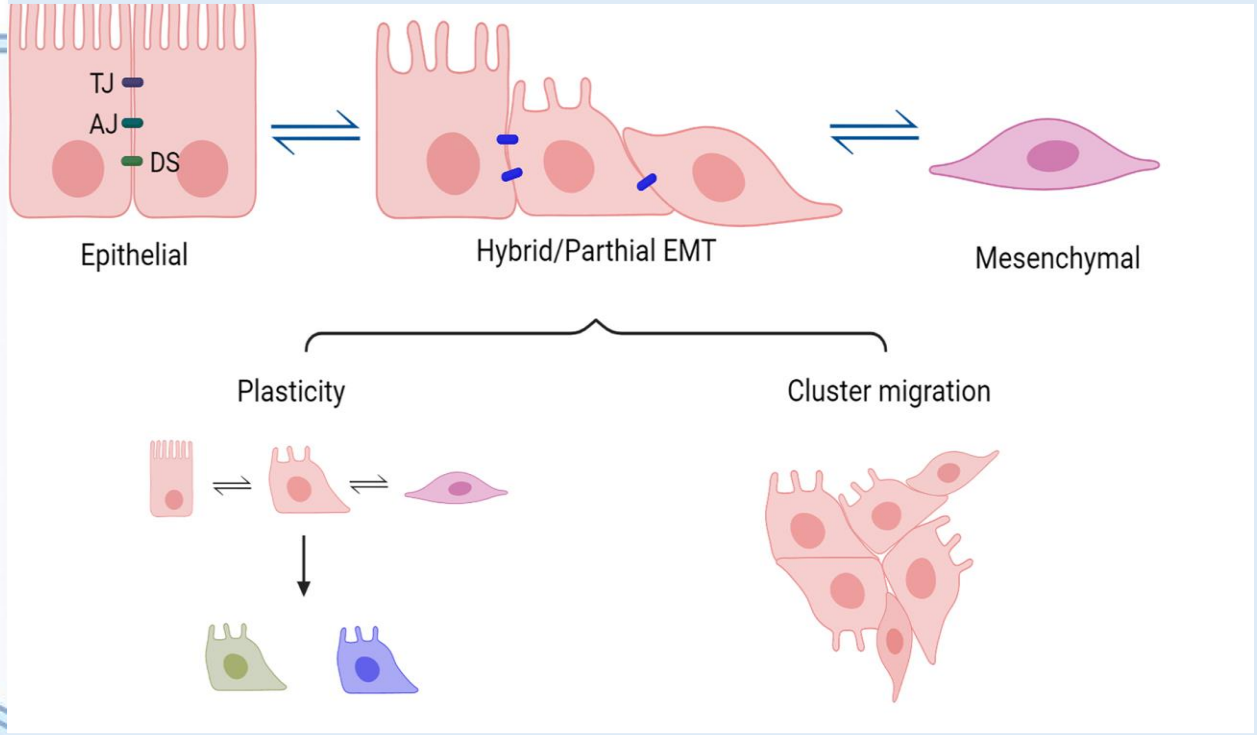
Immunosuppressive Microenvironment


e.
Tryptophan
IDO
Kynurenine
CD8+ T cell
TGF-β
Adenosine
CXCL9/10
TGF-β
CXCL8
Polarization
Monocyte
Tumor vessel

Classic Oncogene Mutation


f.
WNT
RTK
EGFR
PI3K
RAS
PTEN
RAF
AKT
MER
β-catenin
mTOR
ERK/MAPK
Tumor cell


TGFβ
HER2 dimer
HER2/EGFR
P
PI3K/AKT
SMAD2
SMAD3
MH1
MH2
S208
Phosphorylation
at S208 of SMAD3
SMAD4
Cytostasis
EMT,
migration


TJ
AJ
DS
Epithelial
Hybrid/Parthial EMT
Mesenchymal
Plasticity
Cluster migration

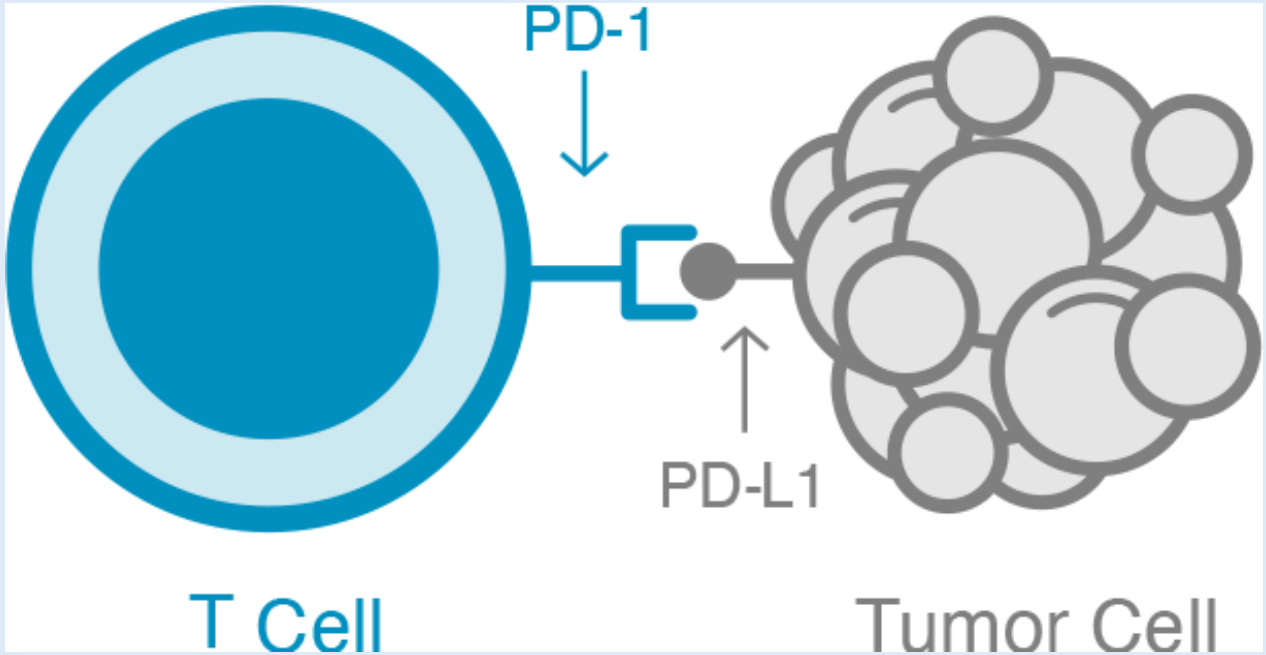
Mechanism of action

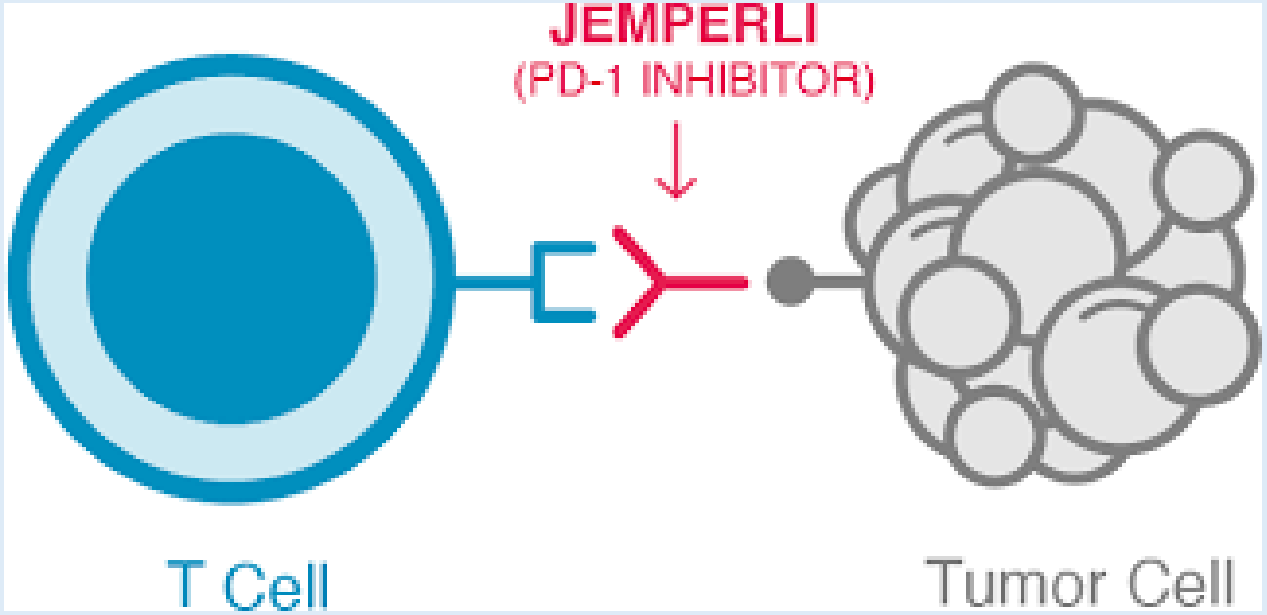
Dostarlimab

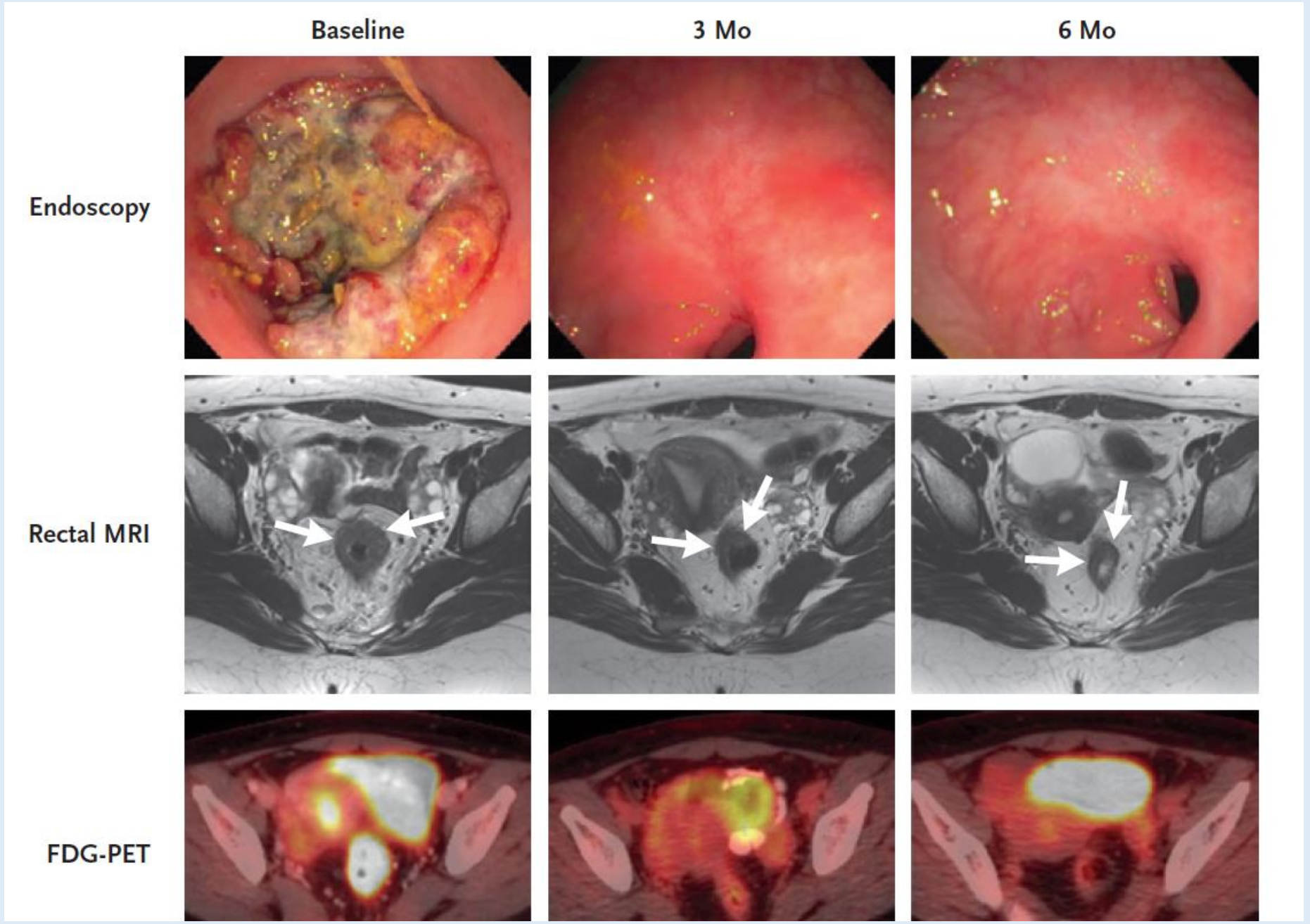
Dostarlimab, sold under the brand name **Jemperli**, is a monoclonal antibody used as a medication for the treatment of endometrial cancer. Dostarlimab is a programmed death receptor-1 –blocking monoclonal antibody.

Formula	$C_{6420}H_{9832}N_{1690}O_{2014}S_{44}$

Mechanism of action


PD-1
PD-L1
T Cell
Tumor Cell


JEMPERLI
(PD-1 INHIBITOR)
T Cell
Tumor Cell


Baseline
3 Mo
6 Mo
Endoscopy
Rectal MRI
FDG-PET

TIMELINE

2020

dostarlimab for reccurent or advancer endometrial cancer

2021

was approved for advanced colorectal cancer with dMMR

2022

reported 100% remission for colorectal cancer

References:

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- https://doi.org/10.1186/s13045-022-01347-8
- doi:10.1038/nri.2017.108
- doi: 10.3389/fcell.2020.00672
- DOI: 10.22034/CAJMPSI.2021.03.02
- doi: 10.3389/fimmu.2017.01597
- doi: 10.3389/fphar.2017.00561

Thank you