HOW TO KILL A MITOTIC CELL:

(1) Targeting microtubules: **TAXANES**

**MOLECULAR MECHANISM OF ACTION:**
Taxanes make microtubules more stable

What do you think the consequences will be for a dividing cell?
TAXANES (MICROTUBULE INHIBITORS)

EXAMPLE: TAXOL (PAXICLATEL)
Isolated from the bark of the yew tree.

MOLECULAR MECHANISM OF ACTION
- Enhances stability of microtubules
- Mitosis blocks at the metaphase-anaphase transition. Prolonged block results in cell death (apoptosis). (Effect depends on drug concentration)

ADVANTAGES
Very effective anti-tumor activity used in treatment of:
* ovarian cancer
* breast cancer
* non small cell lung cancer

DISADVANTAGES
- Severe adverse effects: neuropathies. Microtubules are required for the transport of proteins and vesicles along the axons of neurons.
- Development of resistance: Tubulin mutations.

10^6 patients have been given taxol as part of their chemotherapy regime world-wide.
HOW TO KILL A MITOTIC CELL:

(2) Targeting microtubules: VINCAS

MOLECULAR MECHANISM OF ACTION:
Vincas make microtubules less stable

What do you think the consequences will be for a dividing cell?
**VINCAS (MICROTUBULE INHIBITORS)**

**EXAMPLE:** Vincristine, vinblastine
Isolated from Madagascar periwinkle.

**MOLECULAR MECHANISM OF ACTION**
Inhibits polymerization of microtubules
Blocks mitotic progression.
Prolonged block results in apoptosis (cell death).

**ADVANTAGES**
- Vinblastin used very successfully in combination chemotherapy of Hodgkin’s lymphoma.
- With the introduction of vincristine, the survival rate for children with leukemia jumped from 20 to 80 percent.

**DISADVANTAGES**
- **Severe adverse effects:** neuropathies. Microtubules are required for the transport of proteins and vesicles along axon fibers.

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HOW TO KILL A MITOTIC CELL:

(3) Targeting proteins associated with microtubules (Kinesins): MONASTROL

MOLECULAR MECHANISM OF ACTION:

- Monastrol inhibits the activity of the protein Eg5.
- Eg5 is a kinesin (molecular motor). Its function is to separate the poles of the spindle

What do you think the consequences will be for a dividing cell?
KINESIN INHIBITORS

EXAMPLE: MONASTROL
Selected from a “library” of small molecules.

MOLECULAR MECHANISM OF ACTION
- Inhibits the molecular motor Eg5, responsible for the separation of centrosomes (spindle poles).
- Cells stop in mitosis with monopolar spindles and die by apoptosis (cell death).

ADVANTAGES
- Only effect in dividing cells. No effect on interphase cells.
- No damage to neurons (no neuropathies).

DISADVANTAGES
- Development of resistance (Eg5 mutations).
Targeting proteins that control mitosis (Kinases): **BI 2536**

**MOLECULAR MECHANISM OF ACTION:**
- **BI 2536** inhibits the activity of **Plk1**.
- **Plk1** is a kinase (enzyme). It has multiple functions in mitosis: control of entry into mitosis, formation of bipolar spindle, attachment of the chromosomes to the spindle and cytokinesis.

What do you think the consequences will be for a dividing cell?
KINASE INHIBITORS

EXAMPLE: BI 2536
Selected from a “library“ of small molecules.

MOLECULAR MECHANISM OF ACTION
- Inhibits the enzyme Polo kinase (PLK1), required for: entry into mitosis, formation of the mitotic spindle, attachment of the chromosomes to the spindle and cytokinesis.
- Cells stop in mitosis and die by apoptosis (cell death).


ADVANTAGES
- Only effect in dividing cells. No effect on interphase cells.
- No damage to neurons (no neuropathies)

DISADVANTAGES
- Side effects: Bone marrow suppression. Neutropenia
HOW TO KILL A MITOTIC CELL:
Targeting proteins that control mitosis (Kinases): MLN8237

MLN8237

prophase
prometaphase
metaphase
anaphase
telophase/cytokinesis

MOLECULAR MECHANISM OF ACTION:
- MLN8237 inhibits the activity of Aurora A. Aurora A is a kinase (enzyme). It is required to control entry into mitosis and formation of bipolar spindle.

What do you think the consequences will be for a dividing cell?
KINASE INHIBITORS

EXAMPLE: MLN8237
Selected from a “library” of small molecules.

MOLECULAR MECHANISM OF ACTION

- Inhibits the enzyme Aurora kinase A, required for: entry into mitosis, formation of the mitotic spindle,
- Cells get delayed in mitosis with monopolar spindles; they eventually divide aberrantly. Cell death.

CLINICAL TRIALS: Advanced solid tumors

ADVANTAGES
- Only effect in dividing cells. No effect on interphase cells.
- No damage to neurons (no neuropathies)

DISADVANTAGES
- Side effects: Bone marrow suppression. Neutropenia
HOW TO KILL A MITOTIC CELL:

(5) Targeting proteins that control mitosis (Kinases): ZM447439

MOLECULAR MECHANISM OF ACTION:
- **ZM447439** inhibits the activity of *Aurora B*.
- *Aurora B* is a kinase (enzyme). It is required to control attachment of the chromosomes to the spindle and cytokinesis.

What do you think the consequences will be for a dividing cell?
KINASE INHIBITORS

EXAMPLE: ZM447439
Selected from a “library” of small molecules.

MOLECULAR MECHANISM OF ACTION

- Inhibits the enzyme **Aurora kinase B**. Aurora B is required for multiple processes in mitosis: attachment of the chromosomes to the mitotic spindle and cytokinesis.
- Cells get delayed in mitosis and fail cytokinesis, generating polyploid cells. Cell death.

CLINICAL TRIALS: ZM447439 is not used presently in the clinic. Other Aurora B inhibitors are in clinical trials.

ADVANTAGES
- Only effect in dividing cells. No effect on interphase cells.
- No damage to neurons (no neuropathies)

DISADVANTAGES
- **Side effects**: Bone marrow suppression. Neutropenia