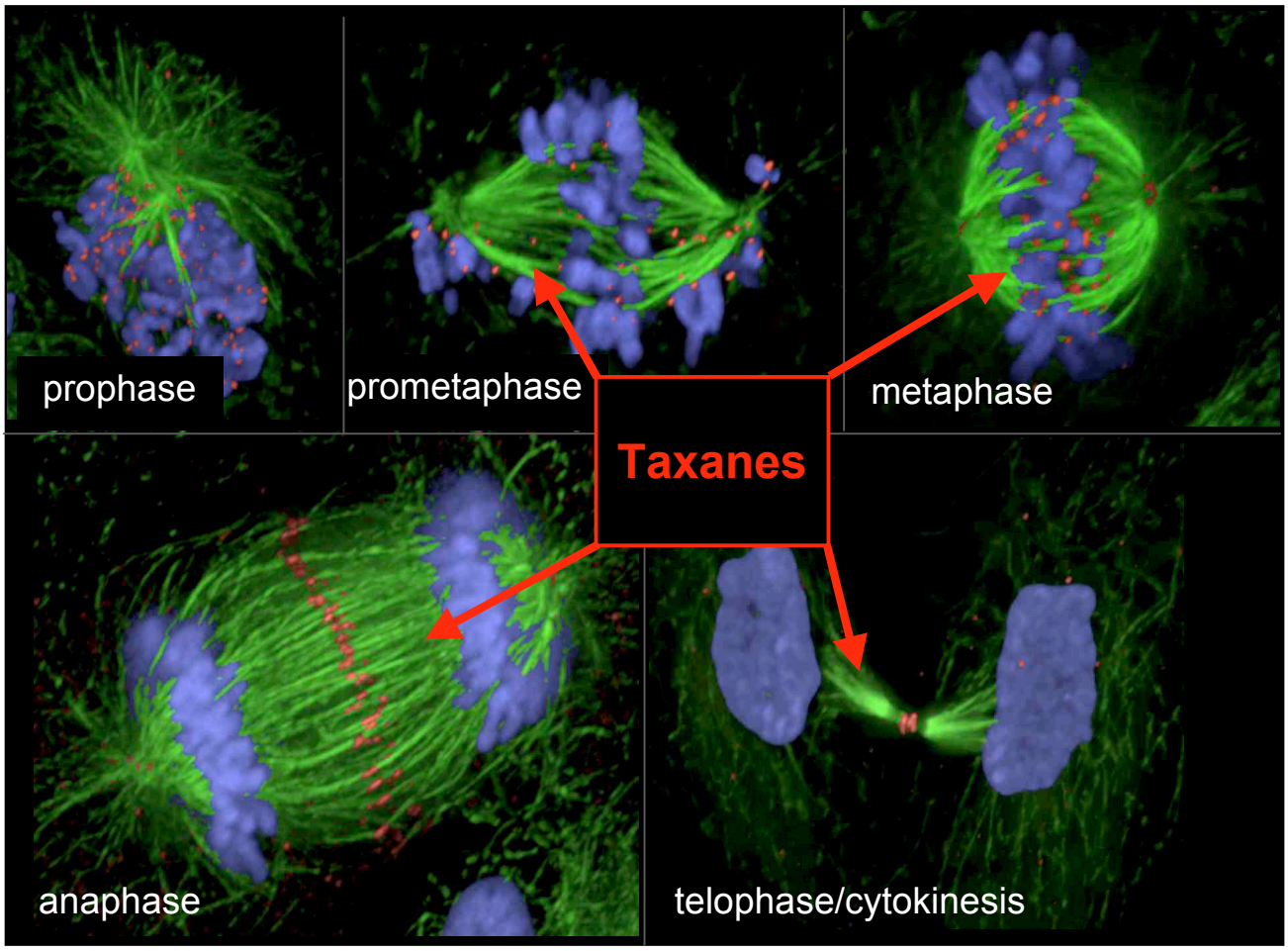
HOW TO KILL A MITOTIC CELL:

(1) Targeting microtubules: **TAXANES**



MOLECULAR MECHANISM OF ACTION:

Taxanes make microtubules more stable

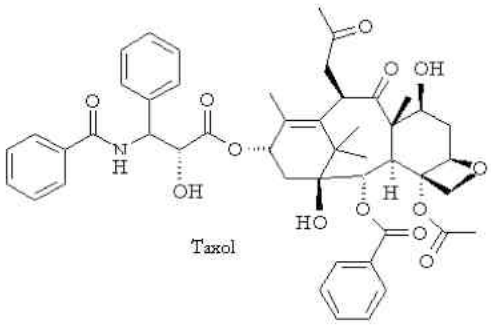
What do you think the consequences will be for a dividing cell?

Mar Carmena

TAXANES (MICROTUBULE INHIBITORS)

EXAMPLE : TAXOL (PAXICLATEL)

Isolated from the bark of the yew tree.



Taxol

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.

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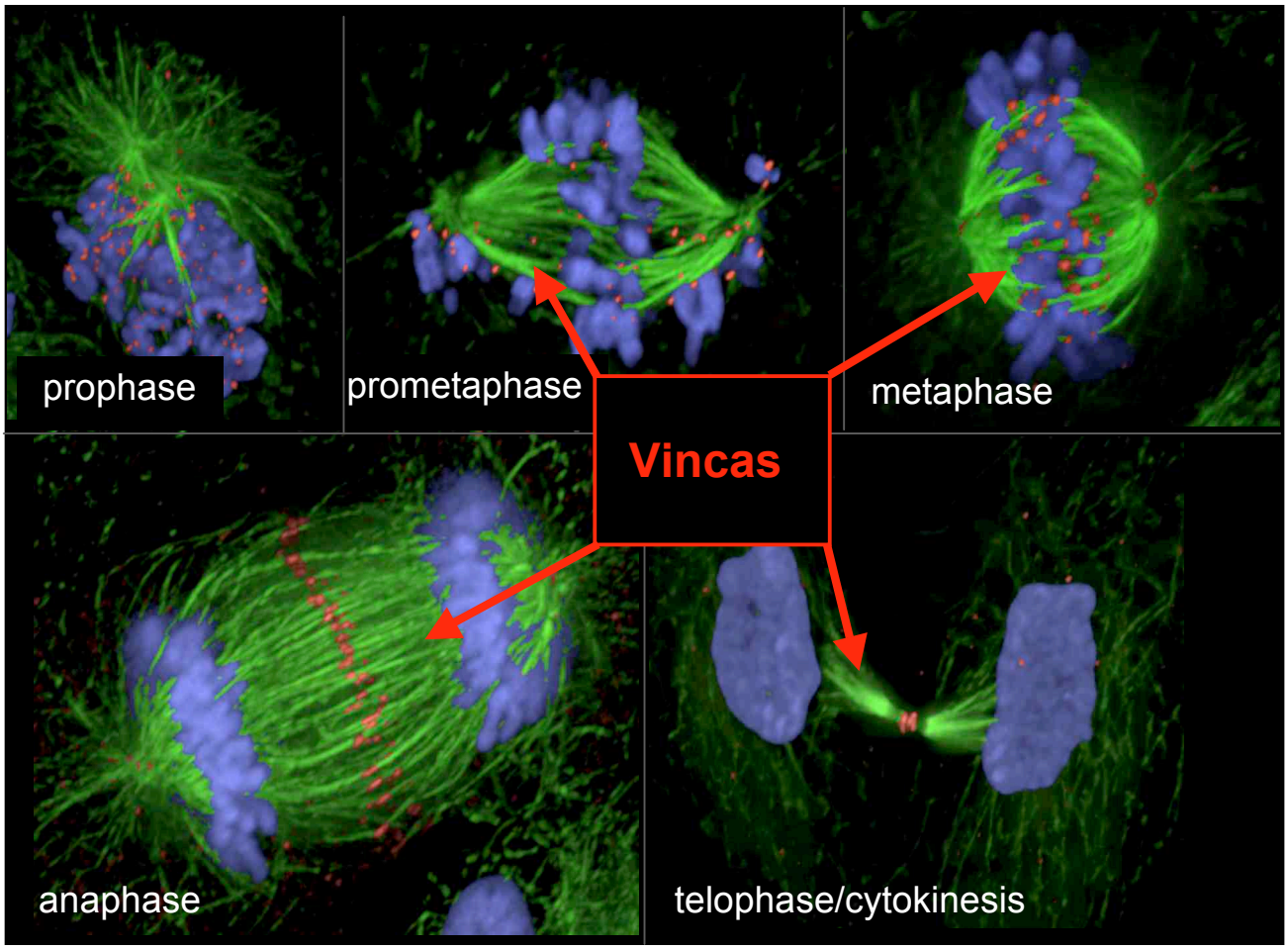
HOW TO KILL A MITOTIC CELL:

(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?

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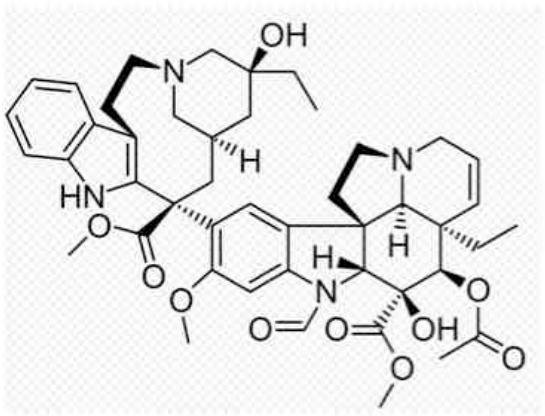
VINCAS (MICROTUBULE INHIBITORS)

EXAMPLE : Vincristine, vinblastine
Isolated from Madagascar periwinkle.



MOLECULAR MECHANISM OF ACTION

Inhibits polylmerization of microtubules
Blocks mitotic progression.
Prolonged block results in apoptosis (cell death).

ADVANTAGES

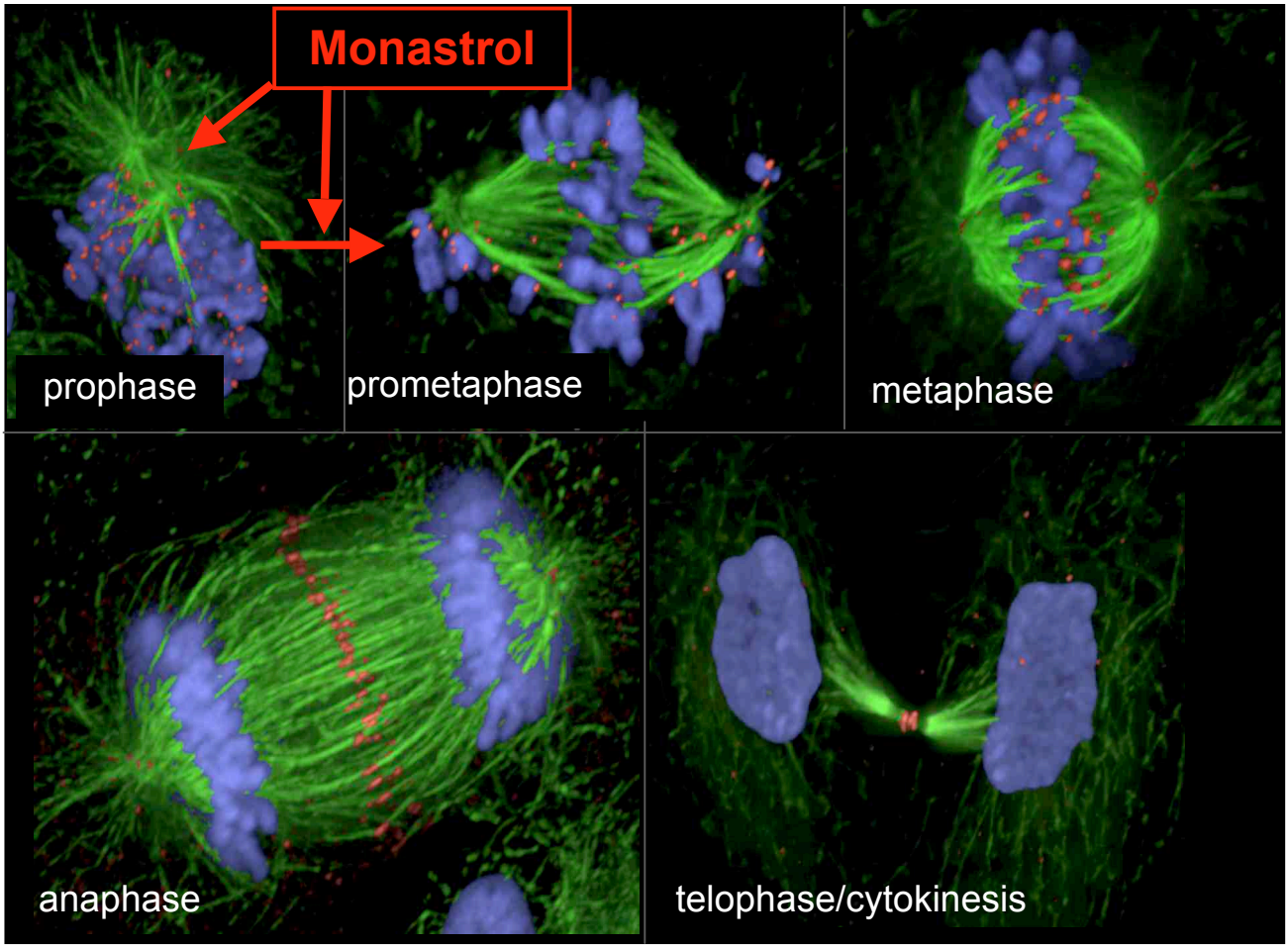
- Vinblastin used very successfully in combination chemotherapy of Hodgkin's lymphoma.
- With the introduction of vincristine, the survival rate for children with leukemia jumped from 20 to 80 percent.

DISADVANTAGES

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

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?

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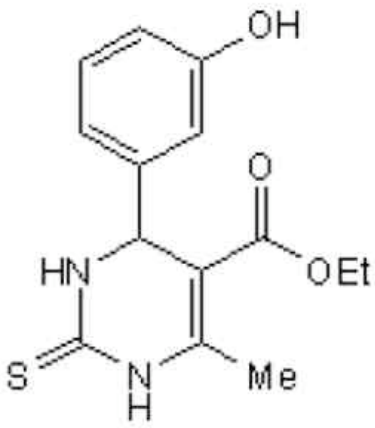
KINESIN INHIBITORS

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).

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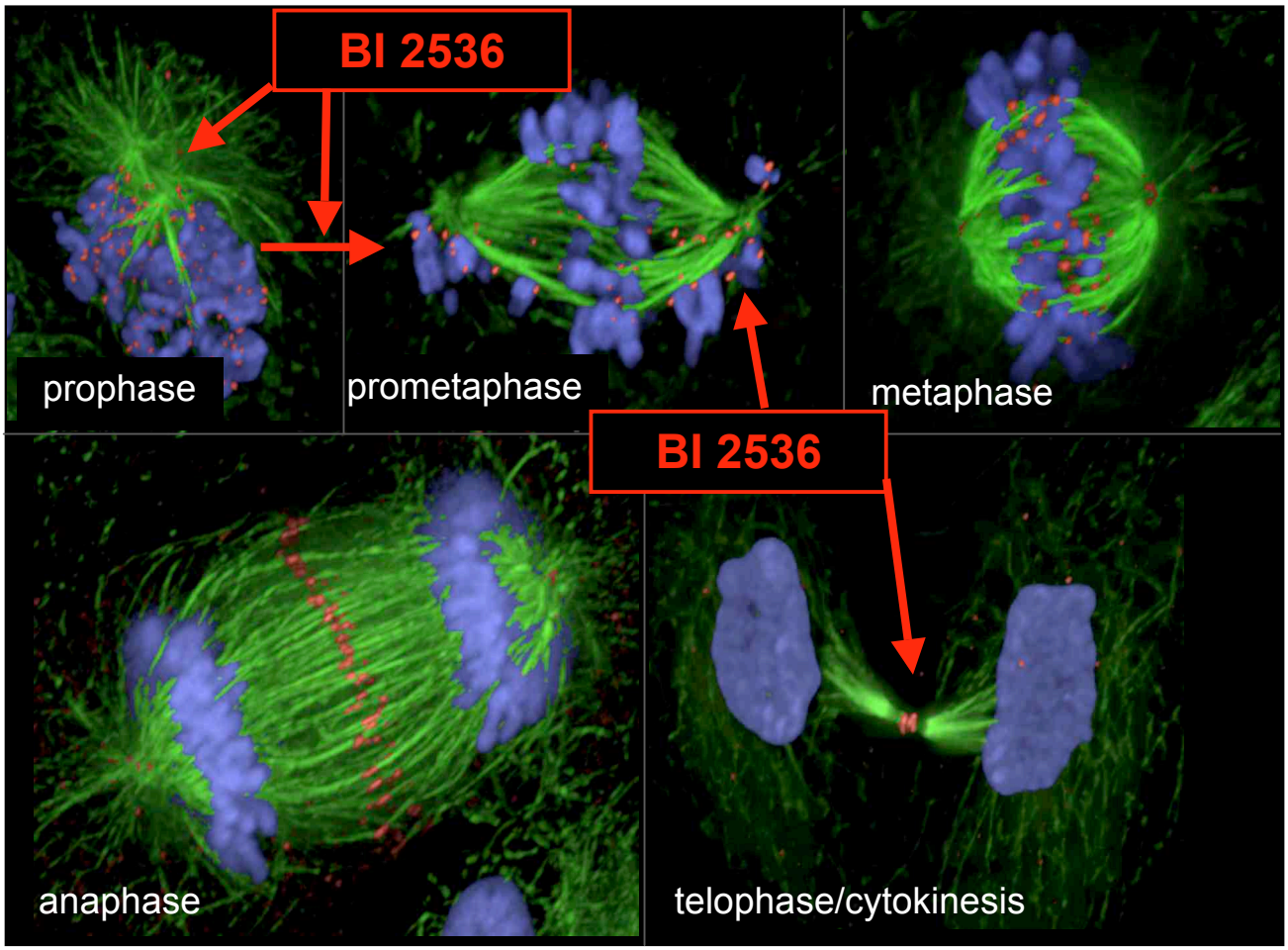
HOW TO KILL A MITOTIC CELL:

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?

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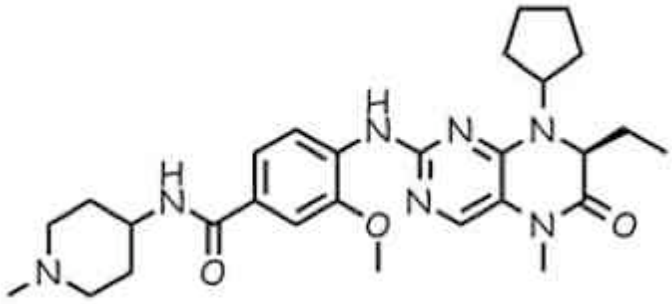
KINASE INHIBITORS

EXAMPLE : BI 2536

Selected from a “library“ of small molecules.



MOLECULAR MECHANISM OF ACTION

- Inhibits the enzyme **Polo kinase (PLK1)**, required for: entry in to 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).

CLINICAL TRIALS: recurrent, metastatic solid tumors. Prostate cancer, advanced pancreatic cancer, Breast Cancer, Endometrial Cancer, Melanoma (Skin), Ovarian Cancer.

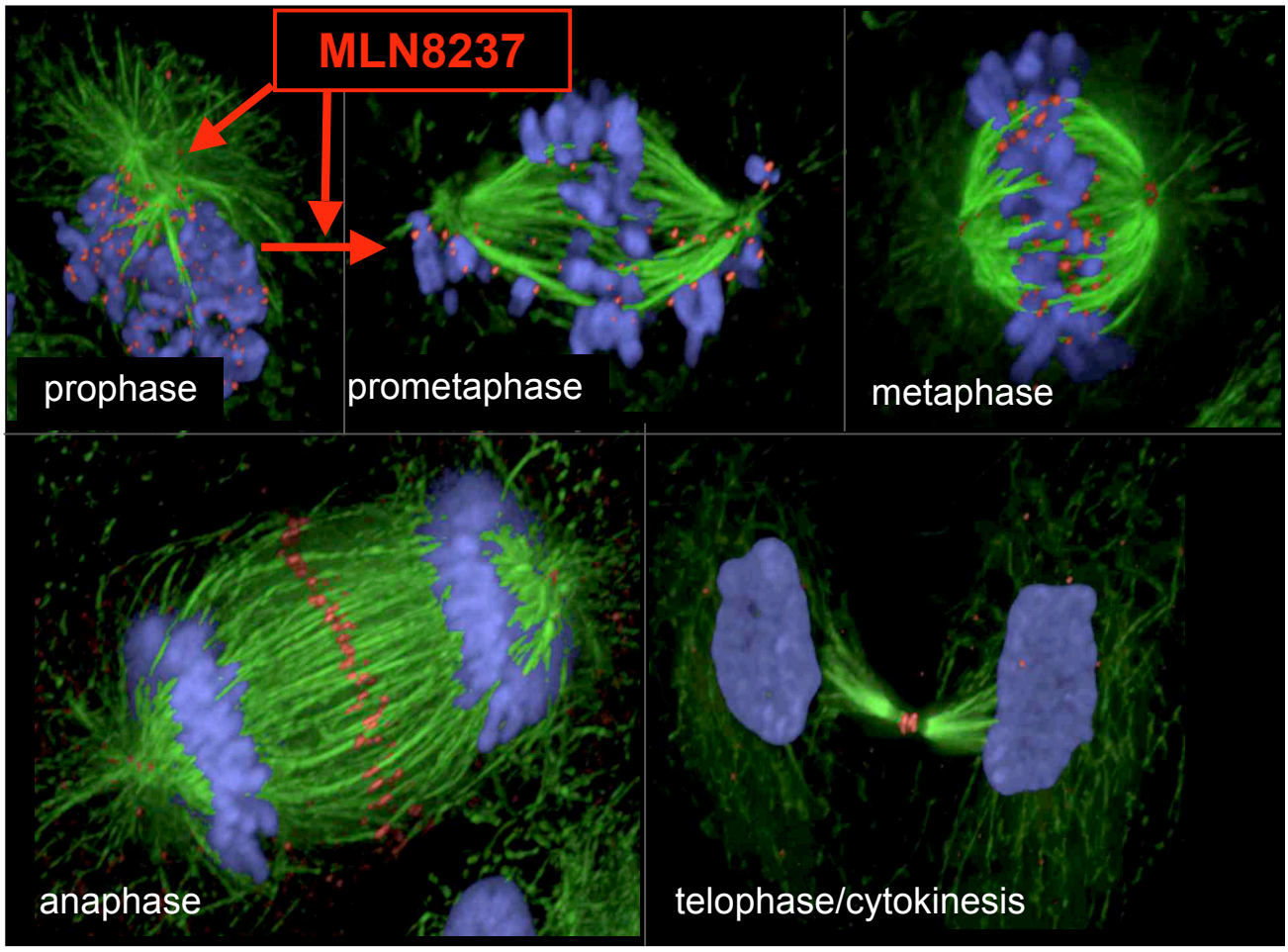
ADVANTAGES

- 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**



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?

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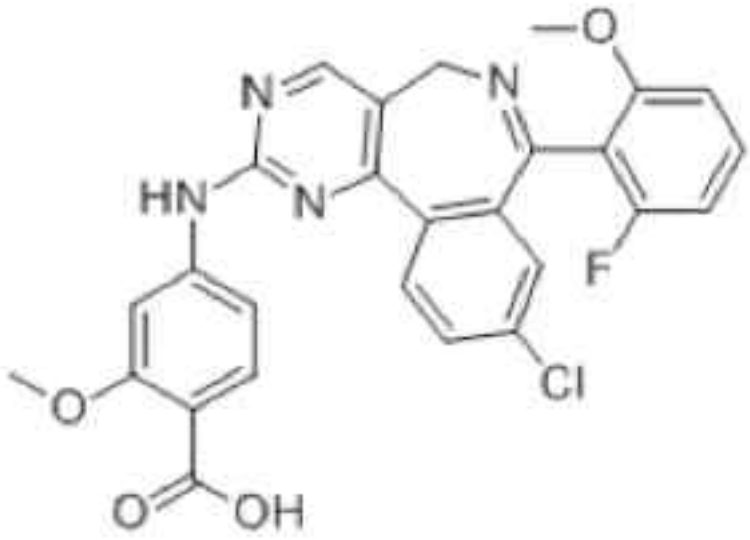
KINASE INHIBITORS

EXAMPLE : MLN8237

Selected from a “library“ of small molecules.



MOLECULAR MECHANISM OF ACTION

- Inhibits the enzyme Aurora kinase A, required for: entry in to 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

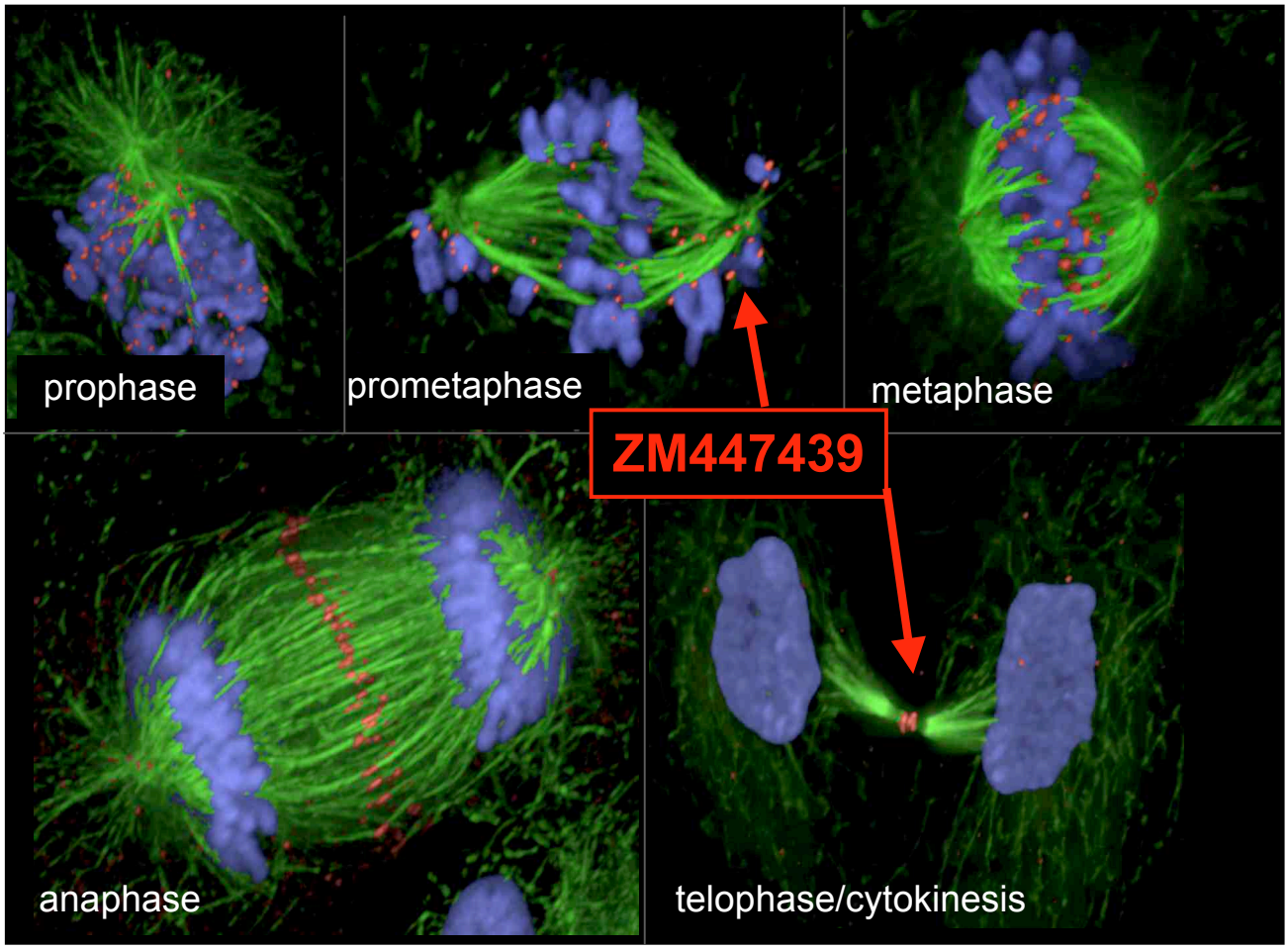
- Only effect in dividing cells. No effect on interphase cells.
-No damage to neurons (no neuropathies)

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?

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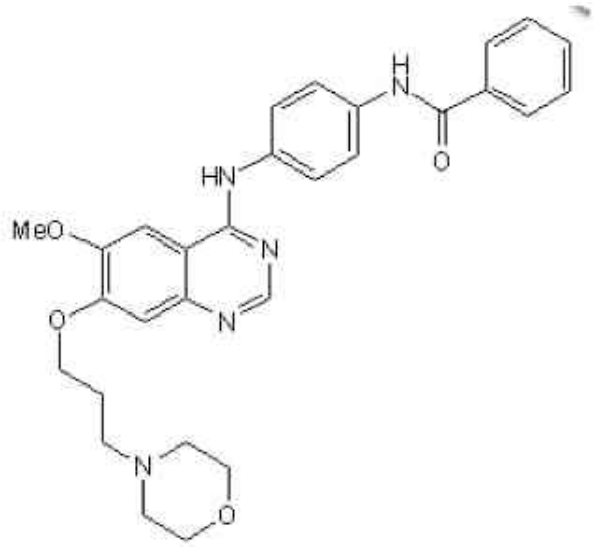
KINASE INHIBITORS

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