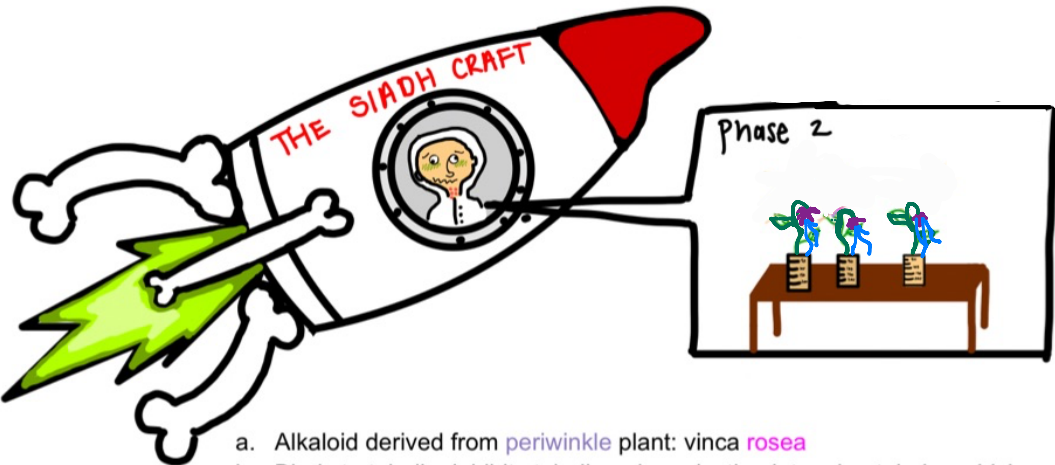


Cancer Chemotherapy 2:

Cell cycle specific (except for doxorubicin, dactinomycin, epirubicin)

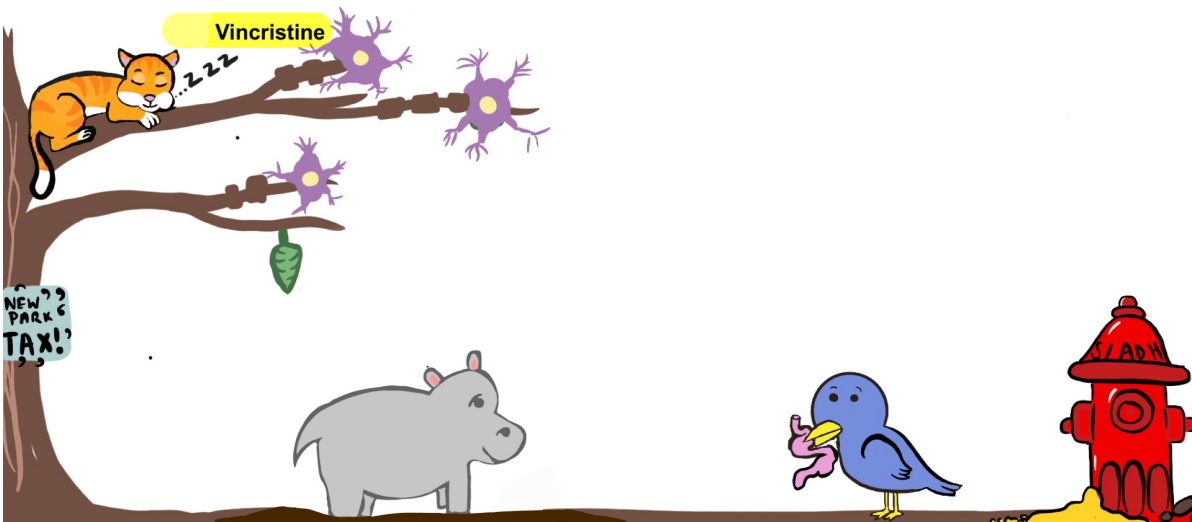
**Natural Products:**

**Vinblastine**



- a. Alkaloid derived from **periwinkle** plant: vinca **rosea**
- b. Binds to tubulin, inhibits tubulin polymerization into microtubules which are a major component of the mitotic spindles
- c. Inhibition mentioned above results in mitotic arrest in **metaphase**, resulting in death
- d. Dose reduction needed in liver dysfunction
- e. **Adverse Effects:**
  - i. N&V
  - ii. Bone marrow suppression
  - iii. Mucositis
  - iv. Syndrome of inappropriate ADH secretion (**SIADH**)
  - v. Alopecia
  - vi. Vesicant and care should be taken during administration

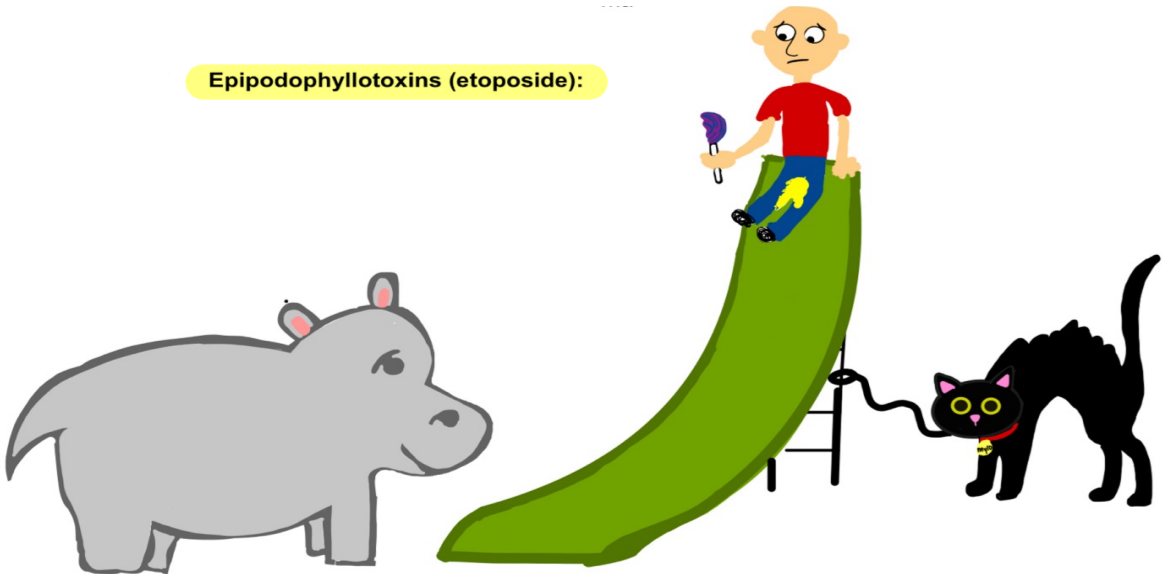
Vin the Astronaut is ready to blast into space (vinblast) he's been preparing his whole life for this moment and has gone bald from stress (alopecia). The trip is a bit shaky so he's getting very nauseous and might even vomit (N&V). The suit he is wearing also seems to be giving him a blistering rash (vesicants). Look at his ship, it looks peculiar, the tip of the aircraft won't get him very far due to its dysfunctional lobe shape (liver dysfunction= different doses). The bone shaped wings of his ship also don't seem very reliable, and will probably suppress him from having a great flight. His fuel seems to have something wrong with it, it has a weird mucous color (mucositis). But lets focus on the bigger picture, he's flying to outer space to see if the rosea periwinkle flower can withstand the temperatures of Neptune. They all seem to not be doing too well because they've all binded to the tubules in the microbes and won't be able to grow to create spindles. Because this mission seems to be failing, vin might not be able to go to phase 2 of his mission(metaphase).



This is chrysalis park where beautiful butterflies lay dormant till they hatch (vincristine). They come here because of the periwinkle rosea plant. Notice how these flowers are shaped very weirdly, almost like neurons (peripheral sensory neuropathy/cranial nerve palsies). This park is also known for its weird creatures that roam around. The city has its own baby hippo that lives here (hypotension)! Many tourists come here all the time but due to the contamination of feces (constipation) and urination (urinary retention) of their pets, there is a tax on the entrance (ataxia). Just look at that firehydrant it is filthy no wonder the SIADH water company put that tax. The sign looks weird tho, it has a bunch of weird symbols that look like commas they might just be scratches from the local cat stray milo (myelosuppression) who enjoys sleeping high in the trees. look at the bird, its gotten its dinner, but because of the contaminated soil, the worm seems to be parasitic and is shaped very oddly like an ileum (paralytic ileus)

- a. Alkaloid derived from **periwinkle** plant: vinca **rosea**
- b. MOA, resistance, and clinical are all identical to vinblastine (mentioned above)
- c. Adverse Effects:**
  - i. Peripheral sensory **neuropathy**
  - ii. Autonomic dysfunction in form of:
    1. orthostatic hypotension
    2. **Urinary** retention
    3. Paralytic ileus
    4. **Constipation**
    5. Cranial nerve palsies
  - iii. Ataxia seizures and coma
  - iv. Mild myelosuppression

## Epipodophyllotoxins (etoposide):



Tommy was at the park and at the top of the slide (etoposide) ready to head down when he saw the local baby hippo at the bottom (hypotension). Notice that the slide is an ugly green vomit color (N&V). Tommy is so scared of the hippo that he's wet himself (dose reduction in renal dysfunction/ excreted by urination). His cat milo (myelosuppression) is tied on the stairs and can't escape the hippo. Notice the stairs are bold on only two sides and makes it look like an II (topoisomerase II). Tommy has the comfort of his half eaten lollipop (50% oral bioavailability). Tommy would have been fine if he had friends to help him but he has none because he gets bullied for his bald head (alopecia).

- a. Extracted from Mayapple root and is a semisynthetic derivative of podophyllotoxin
- b. Oral bioavailability is **50%**
- c. Requires oral dose double that of IV dose
- d. Inhibits DNA synthesis by forming complex with **topoisomerase II** and DNA: which induces breaks in double stranded DNA and prevents repair by topoisomerase II binding
- e. Accumulated breaks in DNA prevent entry into the mitotic phase of cell division, lead to cell death
- f. 30-50% of drug is excreted in **urine**
- g. Dose reduction needed in **renal** dysfunction
- h. Adverse Effects:**
  - i. **N&V**
  - ii. Hypotension
  - iii. Alopecia
  - iv. myelosuppression

## Antitumor antibiotics:

### Note:

- Most are products of various strains of soil microbe: **streptomyces**
- Bind DNA through intercalation between specific bases, block DNA/RNA synthesis, cause DNA strand scission, and interfere with cell replication

### Doxorubicin & Daunorubicin:



The ruby (doxorubicin/ daunorubicin) cave has been deserted due to the toxic waste that's been dumped by the cyt company (cytotoxic anticancer drug). The toxic waste has a gross green puke color (N&V) that has made even the parrot milo bald (myelosuppression & alopecia). There is treasure that hasn't been discovered because no human can enter there even a long lost queen's crown (semiquinone free radicals). There is also scuba gear used for oxygen that has washed up; it seems to be from the brand "free" (free oxygen radicals). There's also a rock that's weirdly shaped like a broken heart (cardiotoxicity). There is also another rock shaped like a lobe (metabolized in liver). On that rock, there's an engraving of S.O.S. but it looks like the "S" wasn't carved correctly so it looks like a 50 (50% dose excreted in bile). The cave looks like it's oozing something green on the top left corner that has to be from the toxic waste (mucositis). The only thing happily living here is the indigenous black widow; look at its web, it looks helical (intercalation to DNA with high affinity)

- Widely used cytotoxic anticancer drugs
- Cytotoxic action is due to:
  - Inhibition of topoisomerase II
  - Intercalation to DNA with high affinity
  - Generation of **semiquinone free radicals**, and **oxygen free radicals**, through iron-dependent, enzyme-mediated reductive process
  - Binding to cellular membrane altering fluidity and ion transport
- Free radicals are the cause of cardiotoxicity in these agents
- IV administration
- Metabolized in liver (reduction and hydrolysis)
- 50% dose excreted in bile
- Dose reduction needed in hepatic dysfunction
- Can be used once every three weeks, low dose weekly, or 3-4 days continuous IV infusion
- Adverse effects:**
  - N&V
  - Myelosuppression (leukopenia > thrombocytopenia)
  - Mucositis
  - Alopecia
  - Acute & chronic **cardiotoxicity** (ECG change, pericarditis, myocarditis, etc)
  - Red urine** (NOT hematuria!)
  - Severe local tissue damage with extravasation
  - Anaphylactoid reactions

## Tyrosine Kinase Inhibitors:

### 1. Imatinib



James has wanted to go to Philadelphia (Philadelphia chromosome) to see his family there but because of the rain storm he has to stop for a bit. Unfortunately he stopped in a rat infested area and now cannot get anywhere because the rats have nibbled on his tires ( imatinib/ tyrosine kinase inhibitor). to make matters worse he's stepped in a puddle and has his shoes and pants soaked (ankle fluid retention). He keep checking his clock because he was supposed to be there at 9 and now its 9:22 (t(9:22)). His glasses are getting really wet as well and he's having trouble seeing the time so he's bringing his arm closer (periorbital edema). He wore his new shirt that shows a broken heart and now its completely ruined (congestive heart failure)

- a. Inhibitor of tyrosine kinase domain of an **oncprotein**; prevents phosphorylation of kinase substrate by ATO
- b. Indicated for treatment of:
  - i. chronic myelogenous leukemia
  - ii. Pluripotent hematopoietic stem cell disorder (characterized by t(9:22) philadelphia chromosome translocation)
- c. Orally absorbed
- d. Adverse Effects:**
  - i. N&V
  - ii. Fluid retention with:
    1. ankles
    2. periorbital edema
    3. Diarrhea
    4. Congestive heart failure
  - iii. Myalgias

# Asparaginase:



The werewolf has been trying to fit in with his fellow humans so he's trying out their food. He's eating asparagus (asparaginase) but it's shaped in L's because he didn't cook them correctly (L-asparagine). He doesn't seem to like them very much and looks nauseous (N&V) he will probably give them to his pet hippo (hypotension). He's shaved his hairy chest to look more human but he's gotten a skin rash because of it (skin rash/urticaria). He'll probably give up and eat his regular meals. There's liver (hepatic toxicity), a pancreas (pancreatitis), a brain (neurologic toxicity), and a pair of lungs (bronchospasm/ respiratory failure). He's washing all this down with a yellow drink, let's hope it's lemonade (renal toxicity).

- Is a L-asparagine amidohydrolase
- Hydrolyzes circulating L-asparagine to aspartic acid and ammonia
- Depletion of L-asparagine causes effective inhibition in protein synthesis
- Note: ALL cells lack whereas normal cells have asparagine synthetase

**e. Adverse effects:**

- Hypersensitivity reactions:
  - Fever; chills
  - N&V
  - Skin rash; urticaria
  - Bronchospasm
  - Respiratory failure
  - Hypotension
- Increased risk of clotting and bleeding
- Pancreatitis
- Renal toxicity
- Hepatic toxicity
- Neurologic toxicity



Peter has turned into a zombie (alemtuzumab) and is being chained up (kappa chain) in the area 52 ( CD52) base for zombies that's located right next to Area 51 for aliens. Notice his weird looking hair they're shaped like b's (b-cell chronic lymphocytic leukemia). He also has a weird new bump growing on the side of his neck where he was bitten and infected (lymphopenia). He's been trying to find the opportunity to escape but is locked deep in the base in case he infects others (opportunistic infections). He's requested a trombone since he used to play when he was human (thrombocytopenia). There's a puddle of blood around his feet and it doesn't seem like it's from anyone other than him, he's losing a lot of blood someone needs to stop the bleeding (neutropenia/ anemia/ thrombocytopenia).

- a. Humanized igG with kappa chain that binds to CD 52 (found in normal and malignant B&T cells, NK, monocytes, macrophages, and small amount of granulocytes)
- b. For treatment of **B-cell chronic lymphocytic leukemia** in patients treated with alkylating agents and failed **fludarabine therapy**
- c. Depletes leukemia and normal cells by **antibody-dependent lysis**
- d. Adverse effects::
  - i. Lymphopenia
  - ii. Neutropenia
  - iii. Anemia
  - iv. Thrombocytopenia
  - v. Opportunistic infections

## Rituximab:



Ritz tux store (rituximab) is currently have a 20% off sale (CD20). The place is so busy that the employee has gone in the back to help customers, unfortunately he's flipped the melena candle (melena) and has set the place on fire ( burning or stinging of skin). The entire front desk has caught on fire as well as the other suits, notice the knobs on the desk they are b shaped (bind to malignant B-lymphocytes). Theres a small patch of fire around the chest of the first suit (chest tightness) which will most definitely spread to the others The fire has set the sprinklers off and has caused the tuxedos to get soaked up. Unfortunately they're soaked around the arms, lower legs, and even has puddled around the bottom feet area (swelling of face, arms, hands, lower legs, or feet). The smoke of the fire will make it difficult for the customers to escape because they'll have trouble breathing (dyspnea). Thank goodness there's a camera (chimeric murine-human monoclonal igG antibody) to capture the carelessness of the employee. theres

- a. Chimeric murine-human monoclonal igG antibody
- b. Binds to **CD20** molecules on normal and malignant **B-lymphocytes**
- c. MOA:
  - i. complement- mediated lysis,
  - ii. antibody-dependent cellular cytotoxicity,
  - iii. induction of apoptosis in malignant lymphoma cells
- d. **Adverse effects**
  - i. Melena; Hematuria
  - ii. Swelling of face, arms, hands, lower legs, or feet
  - iii. Back pain
  - iv. Burning or stinging of skin
  - v. Chest tightness
  - vi. Dyspnea