

Immunosuppression

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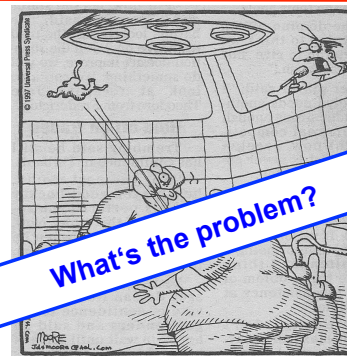
...Let's start



Why immunosuppression ?



Avoid rejection!



Law of Landsteiner adapted to transplantation

		Sera with antibody			
		A	B	AB	O
Red blood cells Donor	A	-	+	-	+
	B	+	-	-	+
	AB	+	+	-	+
	O	-	-	-	-

Solution to ABO barrier

- Transplant blood group compatible
- Living donation
 - Possibility of ABO incompatible transplantation
 - Preparation:
 - Rituximab 4 weeks before Tx
 - Start immunosuppression 2 weeks before Tx
 - Immunabsorption → start usually 5 days before Tx

2. immunological barrier → HLA System

Human leucocyte antibodies
Major histocompatibility complex

Warum sind die Weibchen bei der Partnerwahl so wählerisch? Liebe bei Tupajas

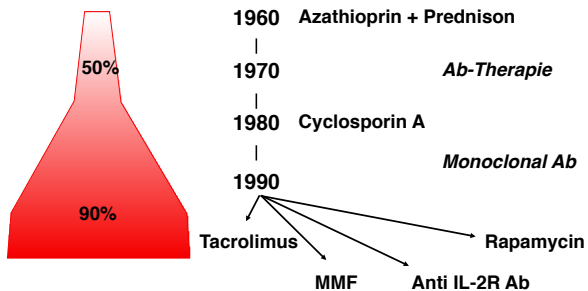


DOI:10.1002/biuz.200910407

LIEBE BEI TUPAJAS | VERHALTEN

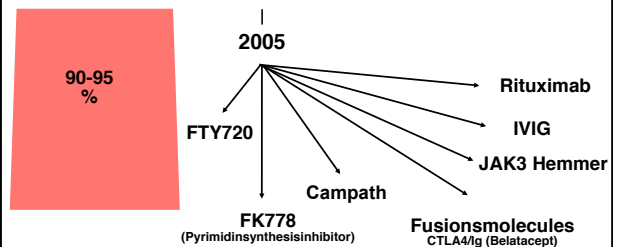
History of immunosuppression

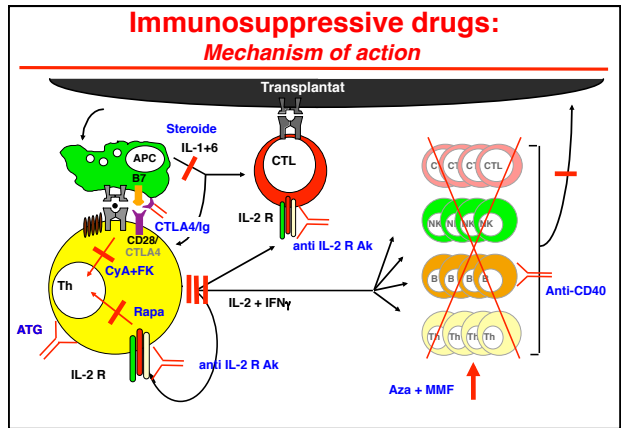
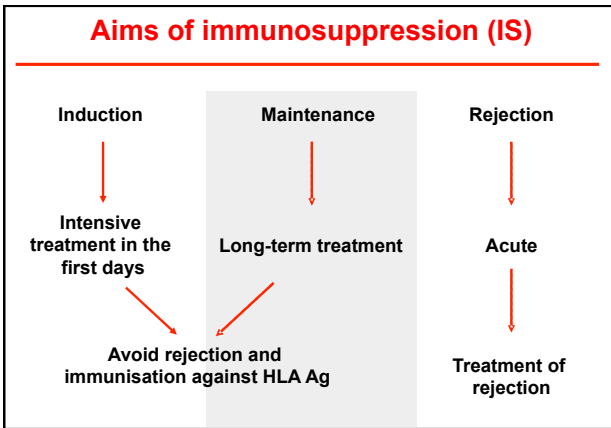
Transplant survival
after one year



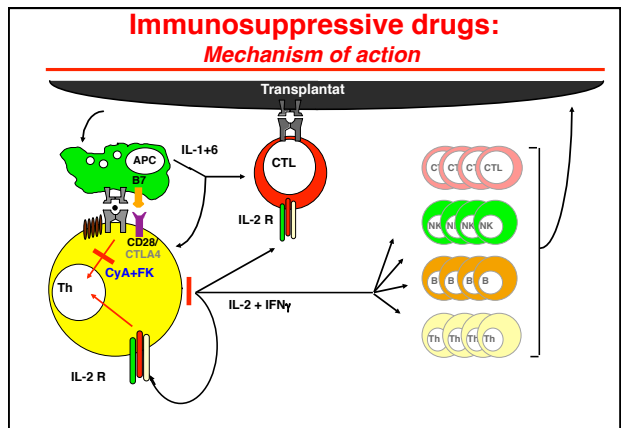
History of immunosuppression

Transplant survival
after one year





Calcineurin inhibitors



Cyclosporine (Sandimmun Neoral®)

Dosage and dose adjustment
Twice daily. Dosage depends on trough levels and immunosuppressive combination

Monitoring by trough levels
12h trough levels or C2 estimation

Cyclosporine (Sandimmun Neoral®)

Side effects

Hyperlipidemia, hypertension, hyperuricemia, gingival hyperplasia, hypetrichosis, tremor

Gingiva hyperplasia under CsA therapy



Hypertrichosis under CsA therapy



Hypertrichosis is a minor side effect

But in a woman or girl it is a huge problem!

Tacrolimus (Prograf®)

Dosage and dose adjustment

Twice daily. Dosage depends on trough levels and immunosuppressive combination

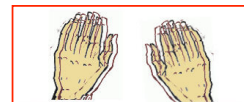
Monitoring by trough levels

12h trough levels

Tacrolimus (Prograf®)

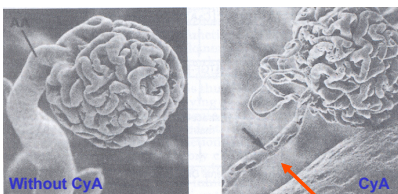
Side effects

Tremor, Diabetes mellitus, hyperlipidemia, neurotoxicity (central and peripheral), sleeping disorders, alopecia, sweating, impaired vision



Calcineurine inhibitor Cyclosporine and Tacrolimus

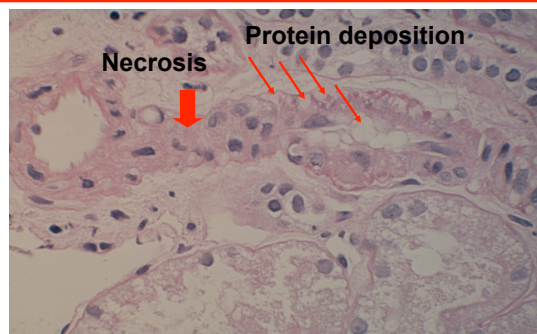
Functional nephrotoxicity



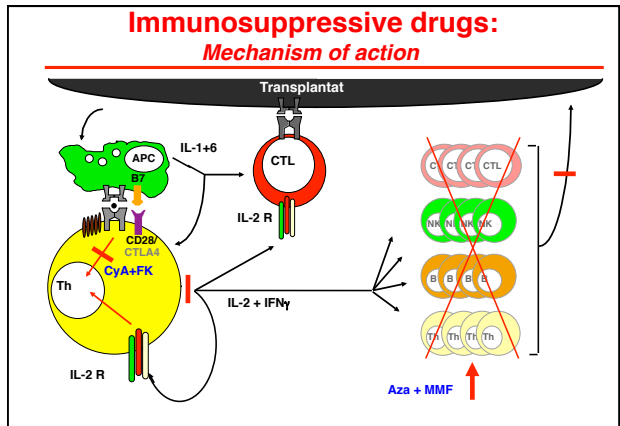
Cyclosporine induced vasoconstriction

English J in Transplantation 1987; 44:135

Vacuolisation and necrosis in arteriols with protein deposition



Azathioprin = Anti metabolites
MMF = Inhibition of purine synthesis



Azathioprine (Imurek®)

Dosage and dose adjustment

Once daily; 2mg/kg (max. 150 mg)
 No trough levels. Monitoring by lymphocyte count
 Reduction in case of side effects

Side effects

Leucopenia, makrocytosis, anemia, thrombocytopenia, infrequently pancreatitis, cholestasis, liver toxicity, alopezia (50%!)

Mycophenolate

Dosage and dose adjustment

Give twice daily, 2 x 1000 mg (CellCept®) or 2 x 720 mg (Myfortic®) .

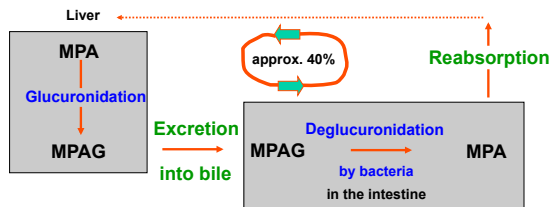
Monitoring

Measurement of trough levels optionally (target > 2 mg/L). Monitor by total blood count

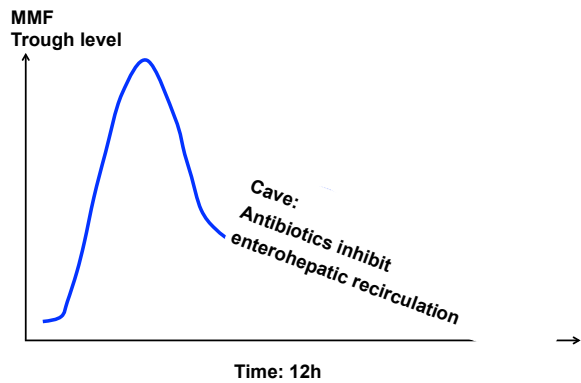
Side effects

Leukopenia, anemia, thrombocytopenia, diarrhoea, flatulence, dyspepsia, elevated liver enzymes, acute hepatitis, herpes infections

Enterohepatic recirculation of MMF
Important → second MMF peak

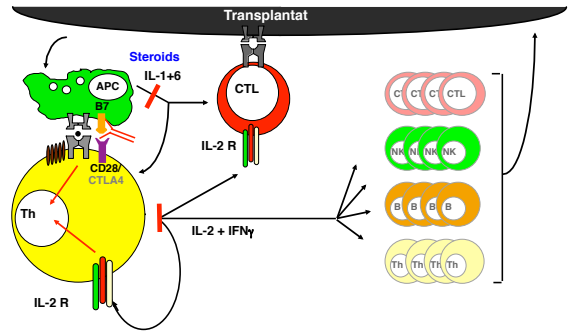


van Gelder T, therapeutic Drug Monitoring. 2001; 23:119-128



Steroids

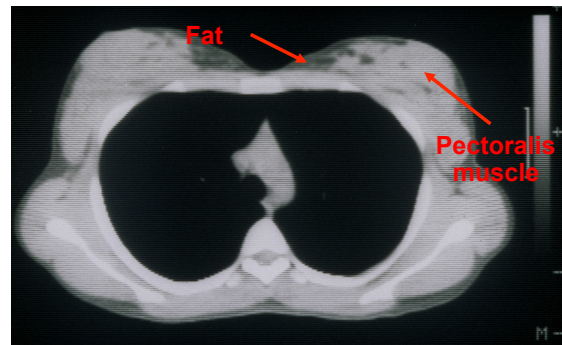
Immunosuppressive drugs: Mechanism of action



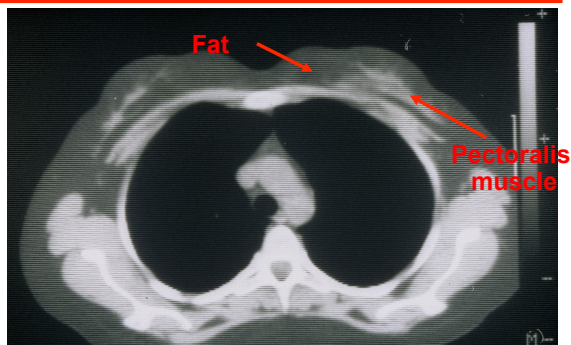
Cushing face and buffalo neck



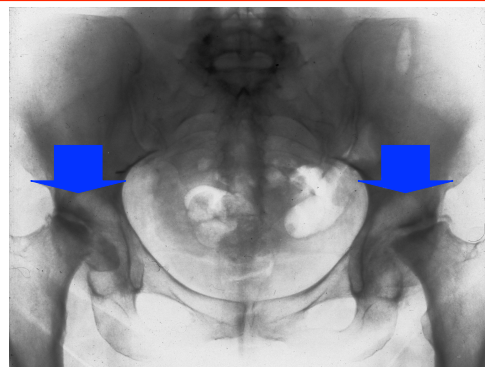
Thorax of a patient starting steroids



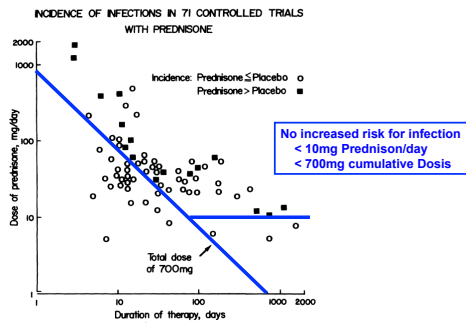
Thorax eines Patienten nach Steroidtherapie



Femoral head necrosis



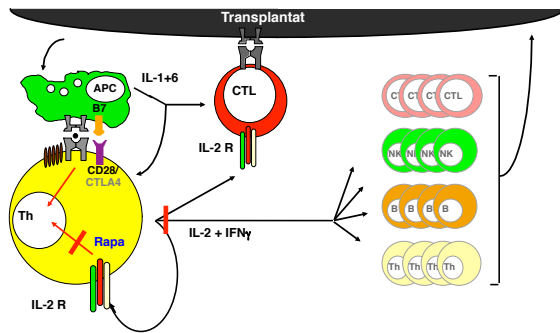
Steroids: how much is relevant for infection?



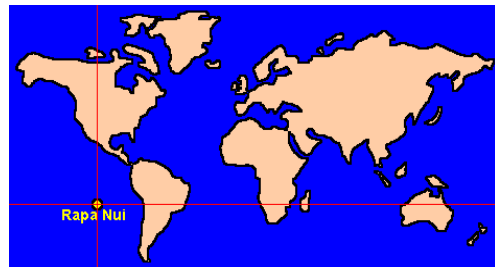
Stuck AE. Rev Infect Dis 1989; 11: 954

Target of Rapamycin Inhibitors

Immunosuppressive drugs: Mechanism of action



TOR inhibitors, where from?



Found in soil samples 1964/65

TOR inhibitors Dosage and dose adjustment

Sirolimus (Rapamune®):

- Once daily, $t_{1/2} > 60$ h: loading dose 10mg, continue with
- Maintenance dose 3mg (1/3 of loading dose)
- Monitor by 12h-trough levels: avoid levels above 10 ng/ml

Everolimus (Certican®):

- Twice daily: 0,75mg
- Monitor by 12h-trough levels: avoid levels above 10 ng/ml

Sirolimus (Rapamune®) und Everolimus (Certican®)

Side effects

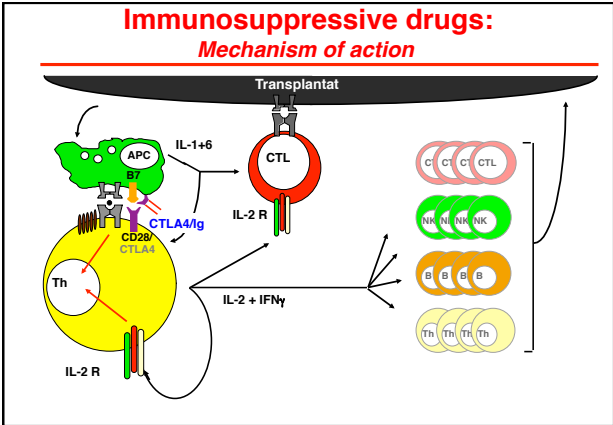
Leucopenia, anemia, thrombocytopenia, microcytosis, hyperlipidemia, acne, ulcerations, tubulo-toxicity, edema, interstitial pneumonitis, arthralgias (reflex sympathetic syndrome)

Anti-proliferative effect ?

- anti-neoplastic effect (Kaposi sarcoma), endocrine tumours
- vascular protection (coronary artery stenting)
- wound healing problems



Belatacept



Belatacept

Mechanism of action
Fusion protein, which acts as a selective T-cell (lymphocyte) costimulation blocker by binding to CD80 and CD86 receptors.

Side Effects
PTLD and various others
Infusion therapy

Induction therapy

- Aim of induction therapy**
-
1. Avoid acute rejection in the first weeks posttransplant = 'more immunosuppression'
 2. Avoid formation of HLA antibodies against the graft
 3. Make transplantation against preexisting donor-specific antibodies in the recipient possible.

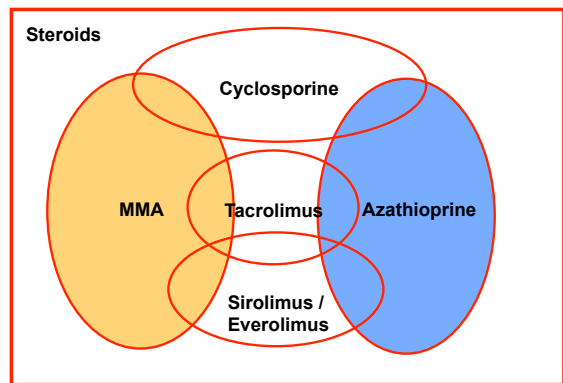
Antibodies

Depleting antibodies	Non-depl. Antibodies	Others
ATG ATGAM OKT-3 Alemtuzumab Rituximab	Daclizumab Basiliximab Eculizumab	Ivlg

Indications for antibodies

Both	Avoid rejection	Eliminate Pre-existing Ab
ATG Thymoglobulin (OKT-3)	Daclizumab Basiliximab Alemtuzumab Eculizumab	Rituximab Ivlg

Which combination?



Current combination of immunosuppression after kidney transplant

1. Methylprednisolon 0.5 g i.v, switch to oral form
2. Tacrolimus (2x1.5mg/kg)
3. Mycophenolat (2 x 1000 mg p.os)

With or without induction: IL-2R Ab (or ATG)



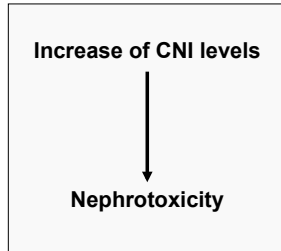
Slow decrease of maintenance immunosuppression
 → taper steroids and decrease trough levels of tacrolimus

Interactions

Cytochrom P450 3A4

Inhibitors

- Makrolide
- Diltiazem
- Valproat
- Azole (Fluconazol...)
- Verapamil
- Floxapen
- Grapefruit



Allgemeine Befunde										
nr.	id	name	Einheit	Wert	Ref	Abw.	Abw.	Abw.	Abw.	Abw.
134	50	1000	ng/ml	179	1000					
135	50	1000	ng/ml	369	1000					
136	50	1000	ng/ml	159	1000					
137	50	1000	ng/ml	629	1000					

Behandlung										
nr.	id	name	Einheit	Wert	Ref	Abw.	Abw.	Abw.	Abw.	Abw.
138	50	1000	ng/ml	160	1000					
139	50	1000	ng/ml	99	1000					

Cytochrom P450

Inductors

- Carbamazepin
- Phenobarbital
- Phenytoin
- Floxapen
- St John's wort

Decrease of CNI levels

↓

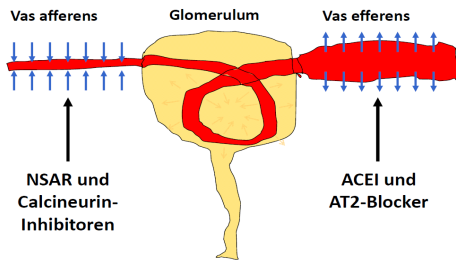
Transplant-rejection

Very frequent interaction

Kidney transplantation and NSAR :
acute hemodynamic renal failure

140	50	1000	ng/ml	228	1000					
141	50	1000	ng/ml	480	1000					

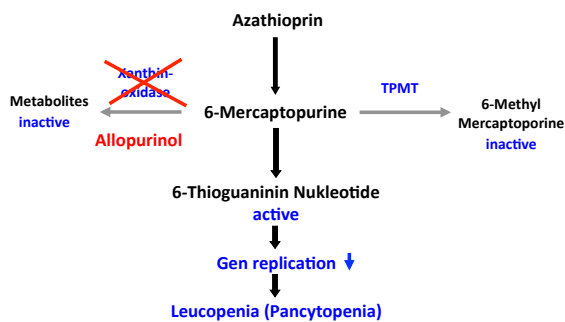
NSAR in kidney transplantation



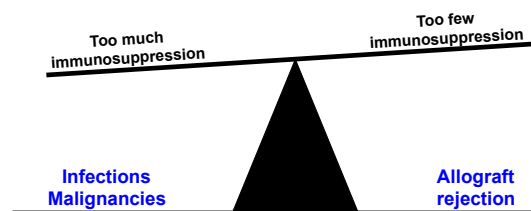
Pain therapy in renal allograft recipients

- **Short time NSAR:**
 - To avoid
 - With good kidney function → can be tried
 - Decline of eGFR has to be expected
- **Solution**
 - Paracetamol
 - Opiates
 - Metamizol
 - Gout: Steroids !!!

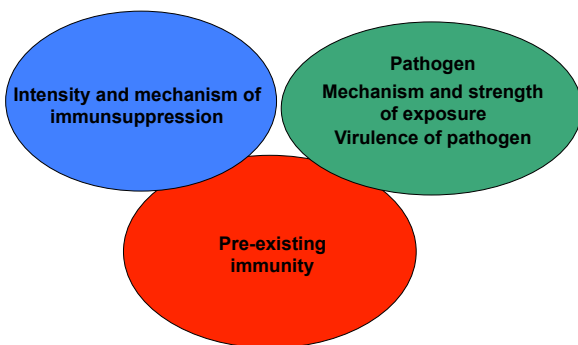
Azathioprin and Allopurinol: Don't do it!



The key problem



What is important to estimate the risk of infection?



What influences the pre-existing immunity?

- Vaccinations
- History of infections: "CMV-status", "EBV-status"...
- Load of earlier immunosuppression (immunological diseases: Vaskulitis ...)
- "Constitution/Co-morbidities": Diabetes....

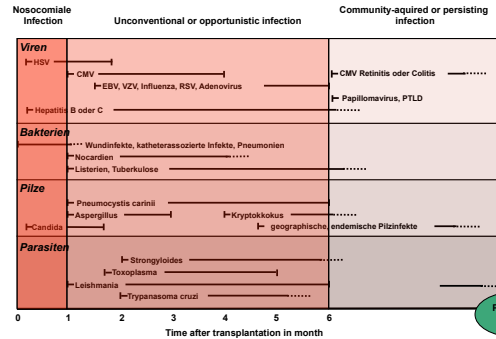


What influences the intensity of immunosuppression?

→ "immunological history"

Intensity and mechanism of immunosuppression

Spectrum of pathogen depends on the timeline of infections after transplantation



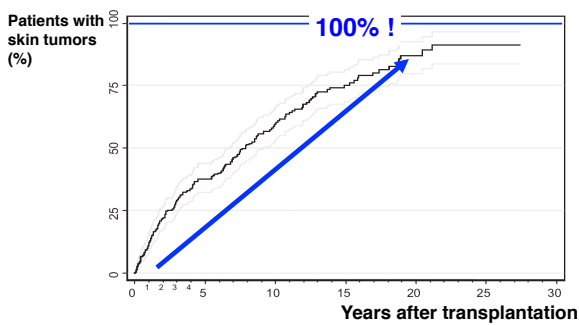
Infections under immunosuppression

- Check history of immunity and immunosuppression
- Check severity of infection
- If possible, always force pathogen identification
- Also late after transplantation „atypical“ infections are to be expected
- Always check if immunosuppression can be reduced

Relative risk of tumors compared with general population

PTLD	40x	↑
Skin-Tumors and Kaposi-Sarkom	20x	↑
Kidney-cell-carcinomas	15x	↑
Melanoma, Leukemia, Hepato-biliary cancers, Cervix und vulvo-vaginale carcinomas	5x	↑
Colon-, lung-, prostate-, stomach, esophagus-, pankreas- and ovarial carcinomas	2x	↑

Risk of skin tumors after organ transplantation (without Melanoma)



What you need to know:

- Principals (combination)
- Possible combinations
- Interactions
- Side effects
- Risk of infections and tumors

