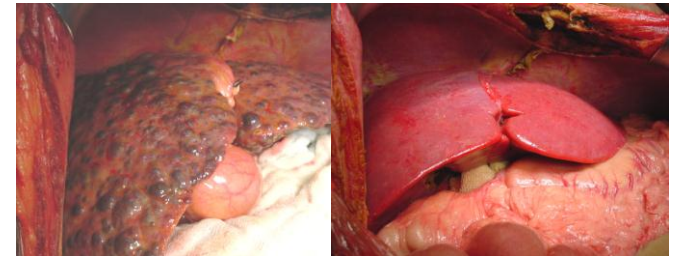




PEDİYATRİK KARACİĞER NAKLİ KURSU: İMMUNOSUPRESYON

*Prof Dr Özlem Durmaz
İ.Ü. İstanbul Tıp Fakültesi
Çocuk Gastroenteroloji, Hepatoloji ve Beslenme Bilim Dalı*



Karaciğer naklinde sağkalım

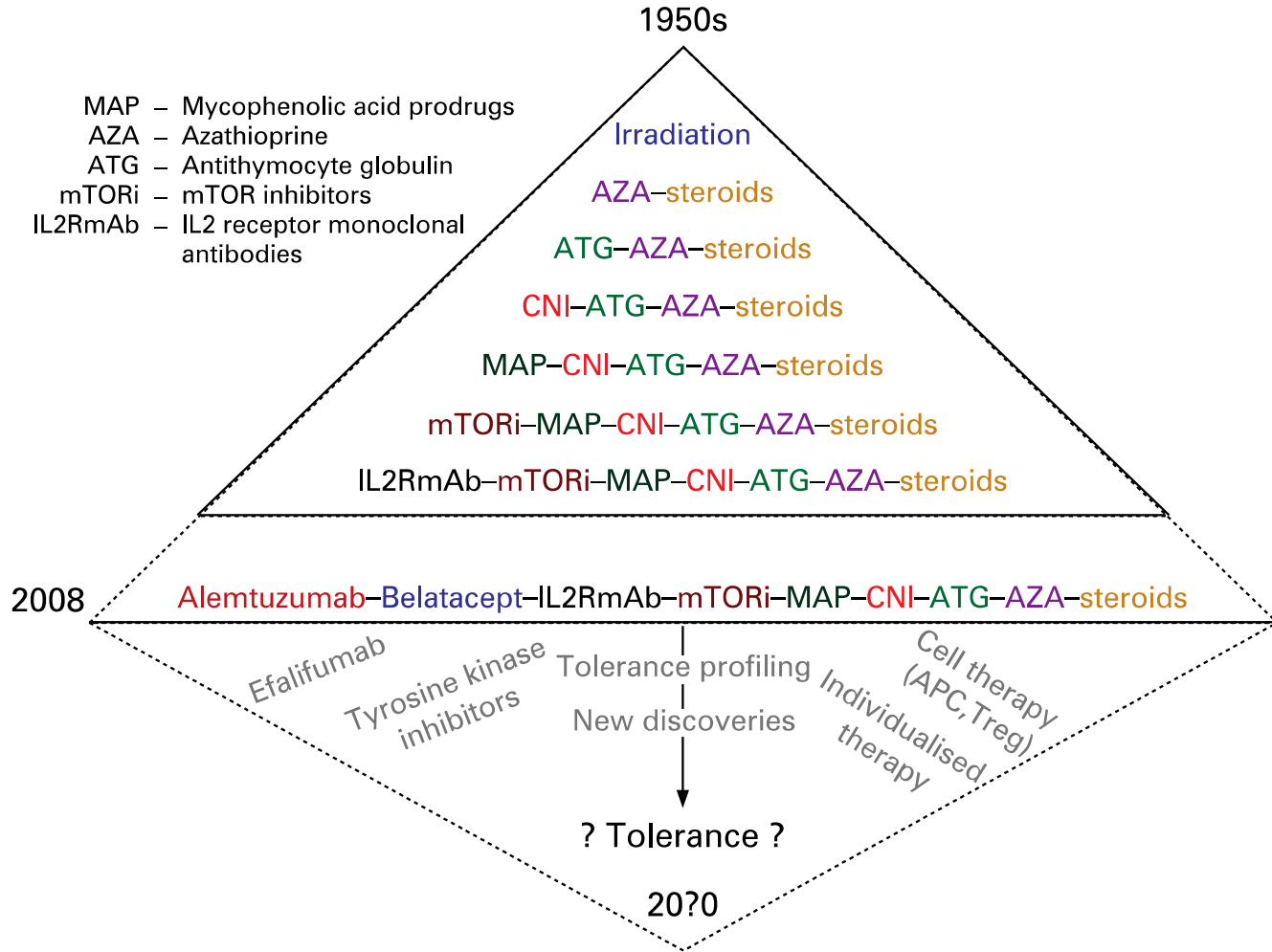
- Cerrahi başarı: 1963 Thomas Starzl (Colorado)

1960-1970'lerde
1 yıllık sağkalım % 30-35

- İmmunolojik başarı:

- ✓ *Allograftın immunolojik* 1980 Siklosporin ve diğer immunosupresyon
- ✓ *Allograft toleransının sağ* 1980-1990'lardan itibaren
1 yıllık sağkalım % 80-90

Evolution of immunosuppression



Organ ve Doku Naklinde İmmünsupresyon- Tanımlar

İNDÜKSİYON İMMÜNSUPRESYONU

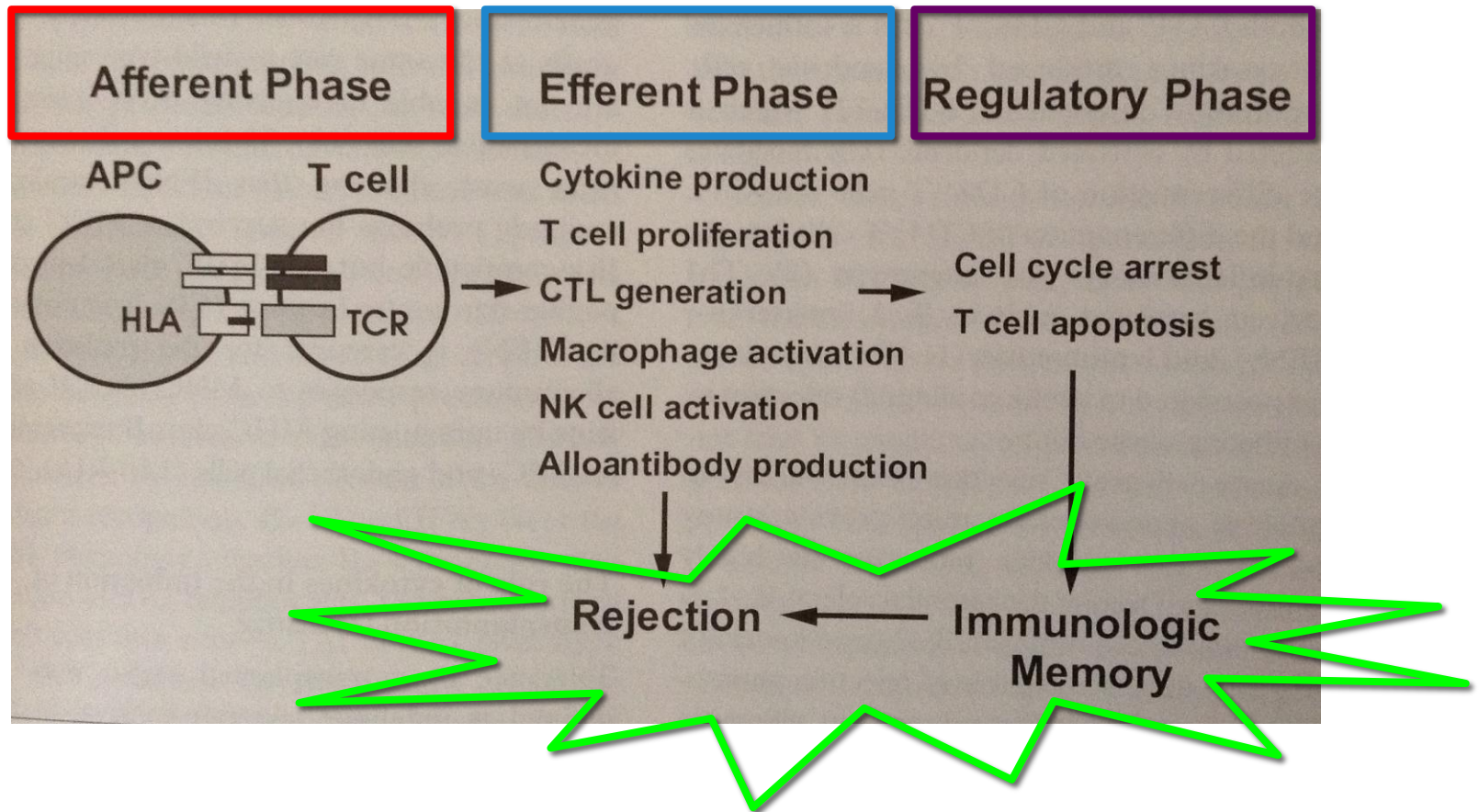
- T hücre aktivasyonunun engellenmesine yönelik
- *T hücre havuzunun depleasyonu*
- *IL-2 salınımının inhibisyonu*

İDAME İMMÜNSUPRESYONU

- T hücre aktivasyonunun / alloimmün yanıtın değişik fazlarında immün yanıtın durdurulmasına yönelik

Karaciğer transplantasyonu sonrası immünsupresif tedavi

Organ naklinde alloimmun yanıtın fazları



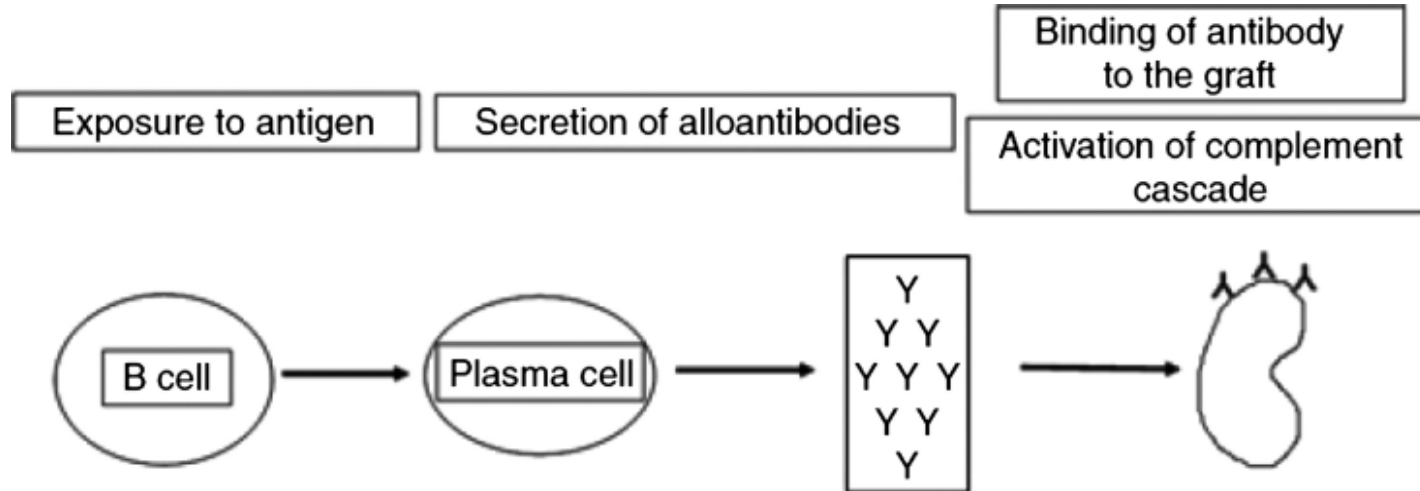
REJEKSİYONUN ÖNLENMESİ VS TOLERANS

Doğal bağışıklık *Innate immunity*

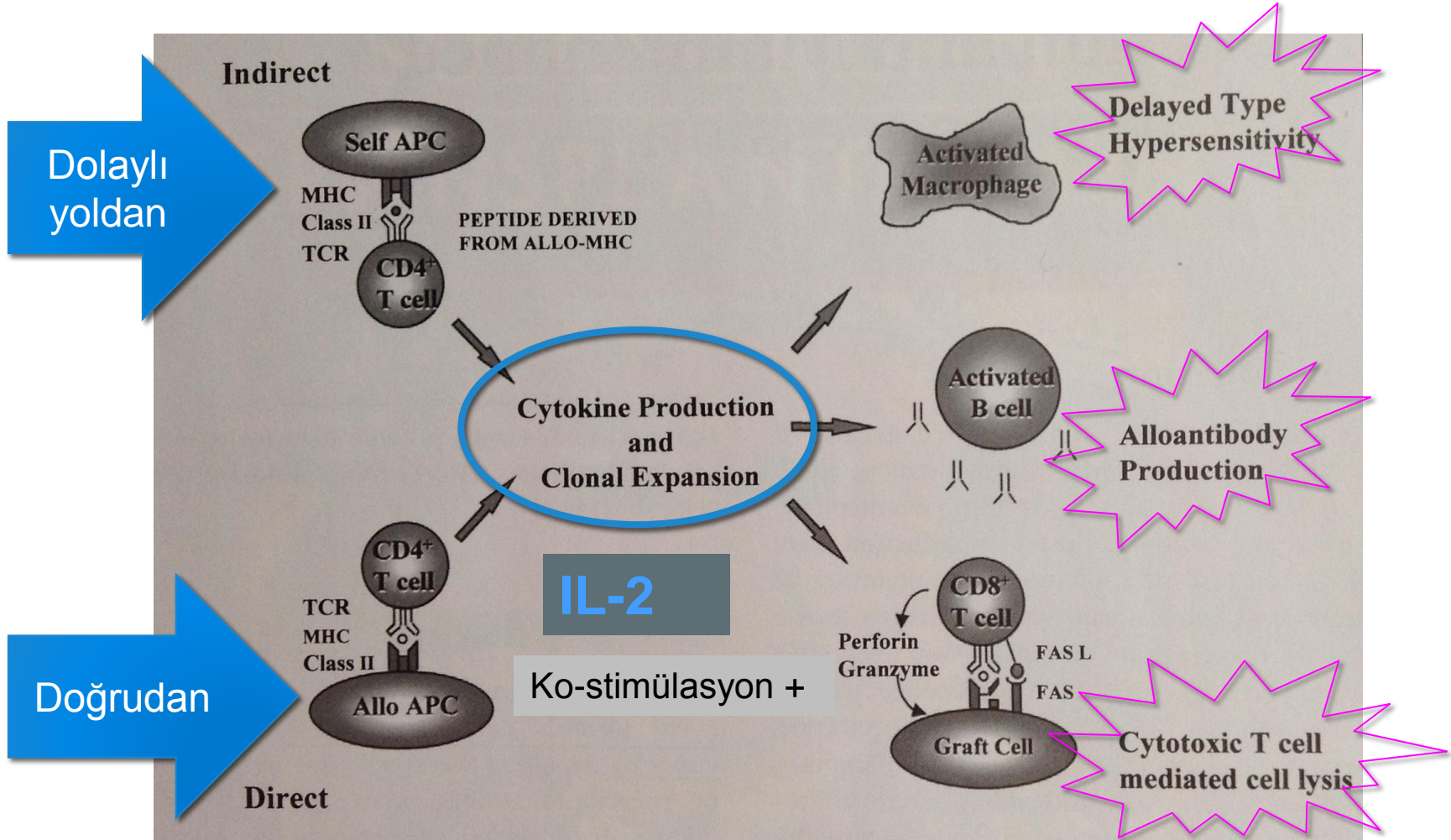
- Anatomik ve fizyolojik bariyerler
- Fagositoz & inflamasyon
(monosit/makrofaj, nötrofil, doğal katil hc (NK), humoral faktörler-kompleman ve lektin gibi opsoninler)

Kazanılmış bağışıklık *Adaptive immunity*

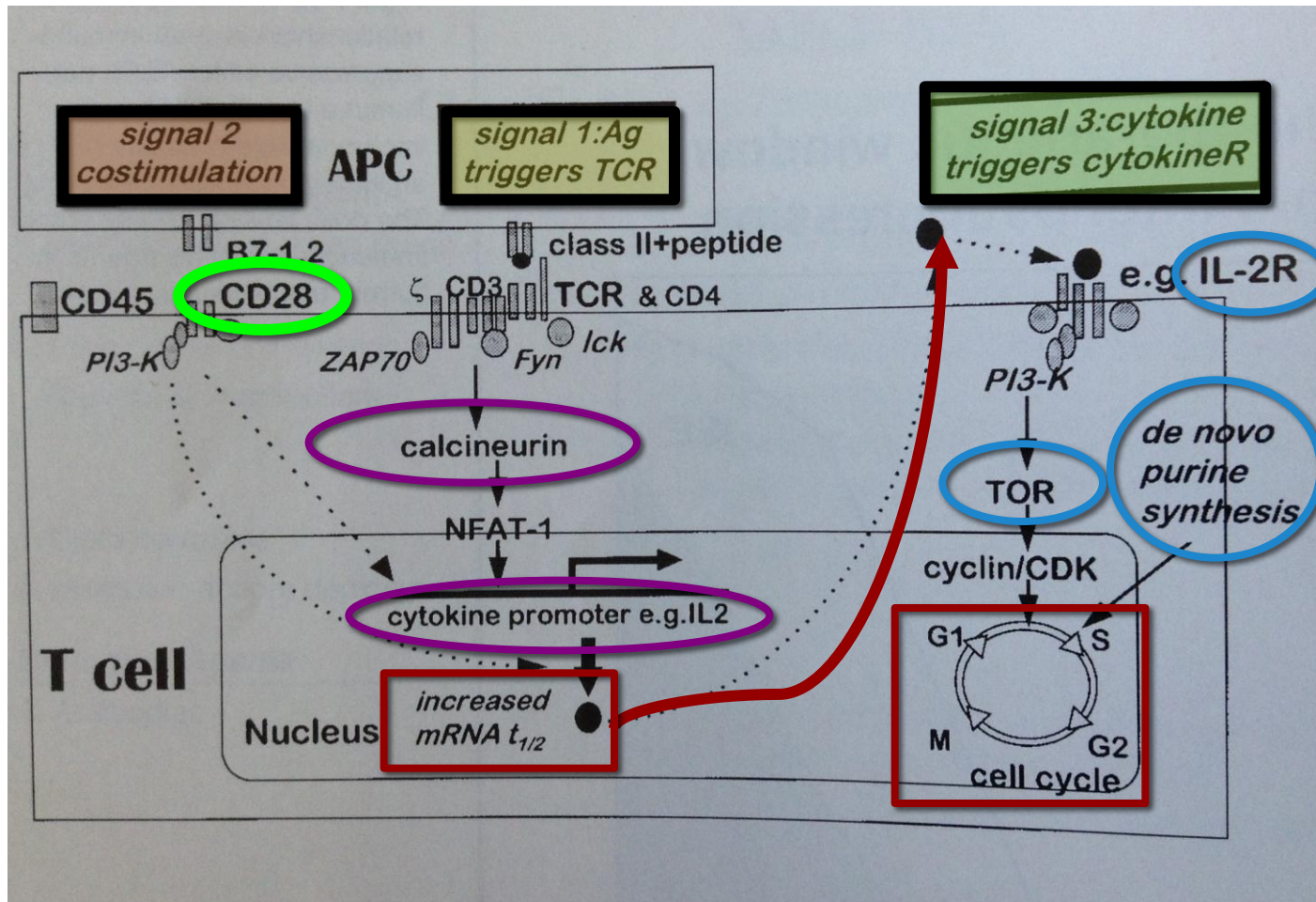
- APCs, dendritik hc'ler
- Efektör lenfoid popülasyonlar
- Humoral antikorlar
- Hc etkileşimini düzenleyen özgün moleküller(sitokin & kemokinler)



Allograft yanıtını oluşturan hücresel etkileşimler



T hücre aktivasyonunun basamakları



İMMUNSUPRESİF İLAÇLAR

yapısal özelliklerine göre

1. Farmakolojik ajanlar
2. Biyolojik ajanlar
3. Fiziksel ajanlar

FARMAKOLOJİK AJANLAR

- İmmunofilin bağlayıcı ajanlar

Kalsinörin inhibitörleri

Siklosporin

FK506

CN'den bağımsız etkili:

Rapamisin

- Hücre bölünmesi / nükleotid metabolizması inhibitörleri

Nonselektif antiproliferatif ve sitotoksikler:

Azatiopurin, siklofosfamid

Lenfosit selektif ilaçlar:

MMF, mizoribin, leflunomid

- Kortikosteroidler
- Diğer

BİYOLOJİK AJANLAR

- Antikorlar

Poliklonal antilenfosit : ATG

Murine monoklonal: anti-CD3 (OKT3), anti-CD4 (OKT4)
anti-LFA, anti-ICAM

Humanize monoklonal (anti-IL2R.....

- Füzyon proteinleri

CTL4Ig, IL-2 toksin

- Sitokin ve sitokin reseptörleri

- Peptid tedavisi

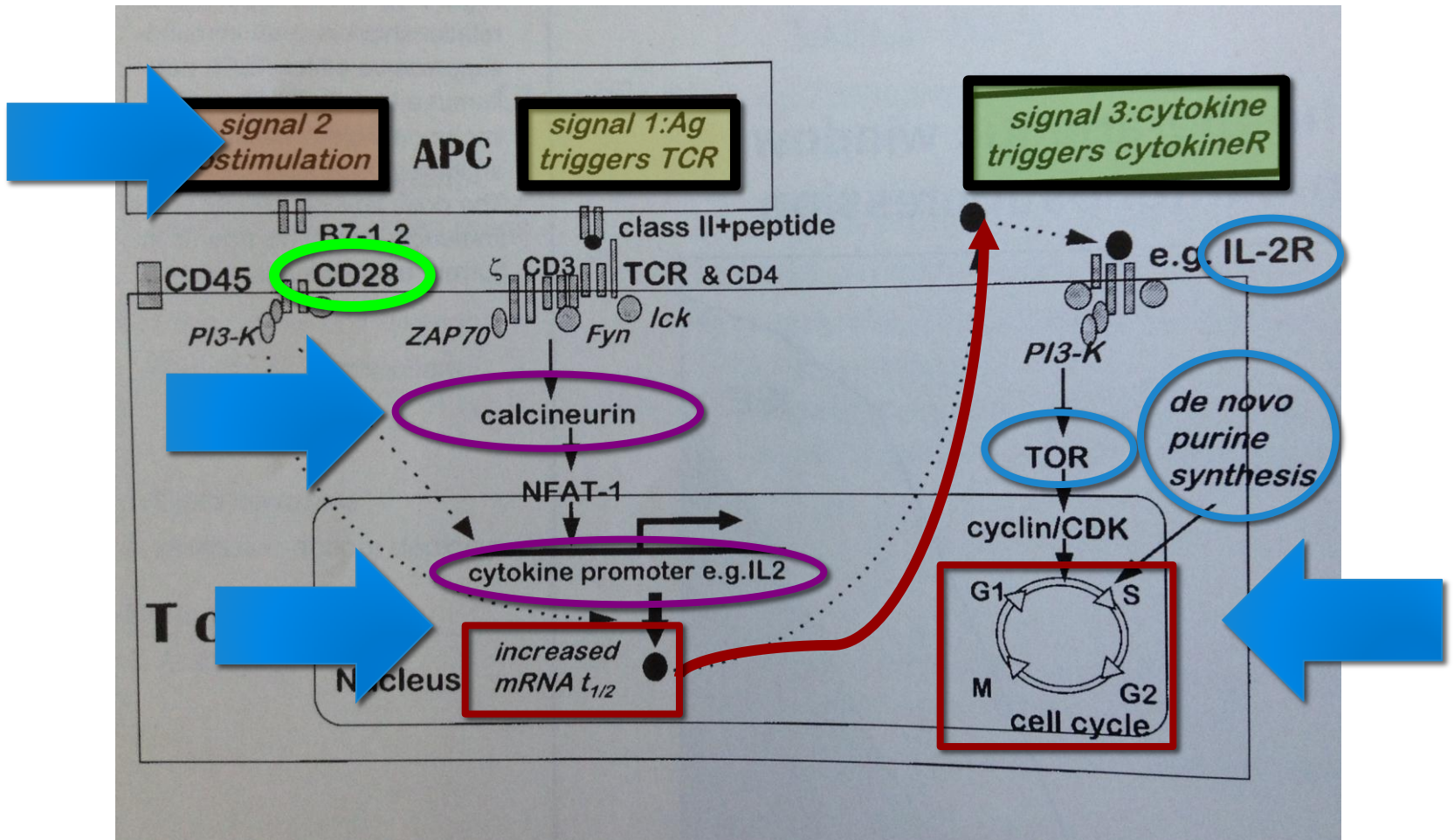
FİZİKSEL AJANLAR

- Radyasyon
- Anatomik / fiziksel manipulasyonlar

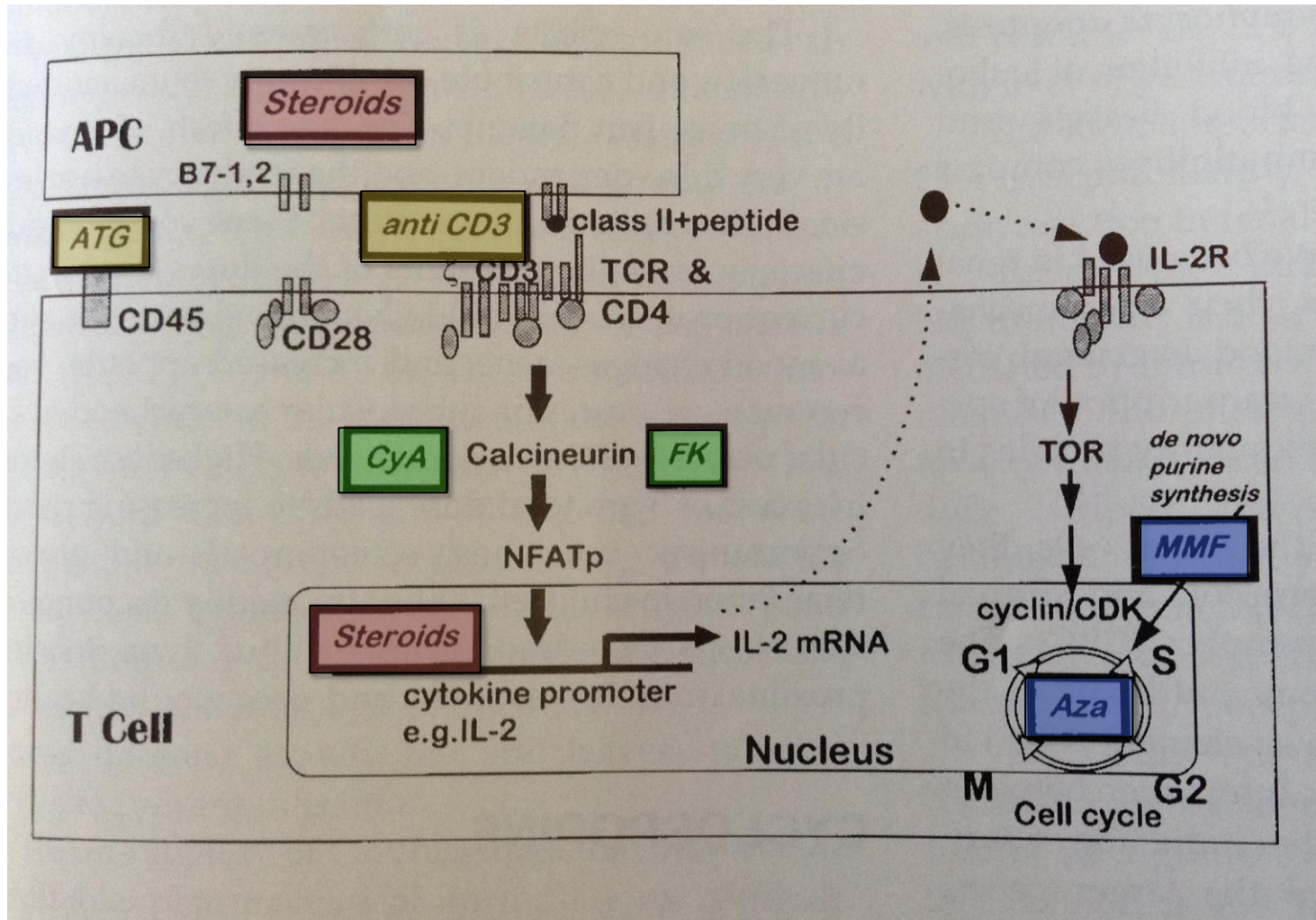
Splenektomi
Plazmaferez
Lökoferez

X ışınları
Ultraviyole

T hücre aktivasyonunun basamakları



Temel immunsupresiflerin T hücre aktivasyonuna etkileri



Etki mekanizmalarına göre immunsupresif sınıfları

Immunosuppressant	Action
T cell activation inhibitors	
Cyclosporine	Inhibits calcineurin via cyclophilin, blocking IL2 transcription
Tacrolimus	Inhibits calcineurin via FKBP12, blocking IL2 transcription
Efalizumab	Non-depleting mAb inhibiting LFA-1 functions, affecting T cell–APC interactions required for T cell activation
Belatacept	CTLA-4 homologue competing with CD28 for CD80/86 binding, inhibiting T cell co-stimulation
T cell depletion	
Anti-thymocyte globulin	Antibody preparation directed against lymphocytes
Alemtuzumab	Anti-CD52 specific antibody highly depletive of lymphocytes, as well as NK cells, monocytes and thymocytes

Etki mekanizmalarına göre immunsupresif sınıfları

Immunosuppressant	Action
T cell proliferation inhibitors	
MPA prodrugs	IMPDH inhibitor: enzyme required for de novo synthesis of guanosine nucleotides, required for lymphocyte proliferation
mTOR inhibitors	mTOR blockade prevents IL2-induced T cell proliferation
Azathioprine	Inhibits purine synthesis, thereby blocking immune cell proliferation
IL2 receptor antibodies	Blocks IL2 engagement and resultant lymphocyte proliferation

İmmünesupresiflerin olumlu/olumsuz etkileri

Agent	Attributes	Negatives/unknowns
Calcineurin inhibitors	<ul style="list-style-type: none"> ▶ Provides reliable protection against rejection ▶ Years of experience with their use 	<ul style="list-style-type: none"> ▶ Renal toxicity ▶ Favourable properties for malignancy ▶ Side effects: diabetes, fibrosis and others
Azathioprine	<ul style="list-style-type: none"> ▶ Inexpensive ▶ Possible anti-hepatitis C virus effects 	<ul style="list-style-type: none"> ▶ Relative weak immunosuppression
Mycophenolic acid prodrugs	<ul style="list-style-type: none"> ▶ Low renal toxicity 	<ul style="list-style-type: none"> ▶ Acute rejection ↑ with monotherapy ▶ Gastrointestinal side effects
mTOR inhibitors	<ul style="list-style-type: none"> ▶ Less renal toxicity than calcineurin inhibitors ▶ Promotion of tolerant state? ▶ Anti-malignancy effect 	<ul style="list-style-type: none"> ▶ Black box warning (sirolimus) for liver transplantation ▶ Side effect: ↓ wound healing, mouth ulcers, hypercholesterolaemia

İmmünesupresiflerin olumlu/olumsuz etkileri

Agent	Attributes	Negatives/unknowns
Calcineurin inhibitors	<ul style="list-style-type: none"> ▶ Provides reliable protection against rejection ▶ Years of experience with their use 	<ul style="list-style-type: none"> ▶ Renal toxicity ▶ Favourable properties for malignancy ▶ Side effects: diabetes, fibrosis and others
Azathioprine	<ul style="list-style-type: none"> ▶ Inexpensive ▶ Possible anti-hepatitis C virus effects 	<ul style="list-style-type: none"> ▶ Relative weak immunosuppression
Mycophenolic acid prodrugs	<ul style="list-style-type: none"> ▶ Low renal toxicity 	<ul style="list-style-type: none"> ▶ Acute rejection ↑ with monotherapy ▶ Gastrointestinal side effects
mTOR inhibitors	<ul style="list-style-type: none"> ▶ Less renal toxicity than calcineurin inhibitors ▶ Promotion of tolerant state? ▶ Anti-malignancy effect 	<ul style="list-style-type: none"> ▶ Black box warning (sirolimus) for liver transplantation ▶ Side effect: ↓ wound healing, mouth ulcers, hypercholesterolaemia

İmmünesupresiflerin olumlu/olumsuz etkileri

Agent	Attributes	Negatives/unknowns
Calcineurin inhibitors	<ul style="list-style-type: none"> ▶ Provides reliable protection against rejection ▶ Years of experience with their use 	<ul style="list-style-type: none"> ▶ Renal toxicity ▶ Favourable properties for malignancy ▶ Side effects: diabetes, fibrosis and others
Azathioprine	<ul style="list-style-type: none"> ▶ Inexpensive ▶ Possible anti-hepatitis C virus effects 	<ul style="list-style-type: none"> ▶ Relative weak immunosuppression
Mycophenolic acid prodrugs	<ul style="list-style-type: none"> ▶ Low renal toxicity 	<ul style="list-style-type: none"> ▶ Acute rejection ↑ with monotherapy ▶ Gastrointestinal side effects
mTOR inhibitors	<ul style="list-style-type: none"> ▶ Less renal toxicity than calcineurin inhibitors ▶ Promotion of tolerant state? ▶ Anti-malignancy effect 	<ul style="list-style-type: none"> ▶ Black box warning (sirolimus) for liver transplantation ▶ Side effect: ↓ wound healing, mouth ulcers, hypercholesterolaemia

İmmünesupresiflerin olumlu/olumsuz etkileri

Agent	Attributes	Negatives/unknowns
Calcineurin inhibitors	<ul style="list-style-type: none"> ▶ Provides reliable protection against rejection ▶ Years of experience with their use 	<ul style="list-style-type: none"> ▶ Renal toxicity ▶ Favourable properties for malignancy ▶ Side effects: diabetes, fibrosis and others
Azathioprine	<ul style="list-style-type: none"> ▶ Inexpensive ▶ Possible anti-hepatitis C virus effects 	<ul style="list-style-type: none"> ▶ Relative weak immunosuppression
Mycophenolic acid prodrugs	<ul style="list-style-type: none"> ▶ Low renal toxicity 	<ul style="list-style-type: none"> ▶ Acute rejection ↑ with monotherapy ▶ Gastrointestinal side effects
mTOR inhibitors	<ul style="list-style-type: none"> ▶ Less renal toxicity than calcineurin inhibitors ▶ Promotion of tolerant state? ▶ Anti-malignancy effect 	<ul style="list-style-type: none"> ▶ Black box warning (sirolimus) for liver transplantation ▶ Side effect: ↓ wound healing, mouth ulcers, hypercholesterolaemia

İmmünesupresiflerin olumlu/olumsuz etkileri

Agent	Attributes	Negatives/unknowns
Steroids	<ul style="list-style-type: none"> ▶ Broad spectrum of effects ▶ Reverses refractory acute rejection 	<ul style="list-style-type: none"> ▶ Risk of hepatitis C virus re-infection ▶ Side effects: diabetes, obesity, osteoporosis
Thymoglobulin	<ul style="list-style-type: none"> ▶ Avoidance of renal toxicity ▶ Promotion of Treg expansion/tolerance 	<ul style="list-style-type: none"> ▶ Possible severe adverse reaction ▶ Must be used with added immunosuppression/short-term use
Interleukin 2 receptor antibody	<ul style="list-style-type: none"> ▶ Avoidance of renal toxicity 	<ul style="list-style-type: none"> ▶ Must be used with added immunosuppression/short-term use
Alemtuzumab	<ul style="list-style-type: none"> ▶ Specific effect on activated T cells ▶ Avoidance of renal toxicity ▶ Potential for re-setting the immune system ▶ Depletes cells from blood and lymph nodes 	<ul style="list-style-type: none"> ▶ Possible interference with tolerance induction? ▶ Must be used with added immunosuppression/short-term use ▶ Long-term effects of depletion still unknown
Belatacept	<ul style="list-style-type: none"> ▶ Avoidance of renal toxicity ▶ Need to administer only once a month 	<ul style="list-style-type: none"> ▶ Must be used with added immunosuppression ▶ Effects in recipients of liver transplantation are unknown

İmmünesupresiflerin olumlu/olumsuz etkileri

Agent	Attributes	Negatives/unknowns
Steroids	<ul style="list-style-type: none"> ▶ Broad spectrum of effects ▶ Reverses refractory acute rejection 	<ul style="list-style-type: none"> ▶ Risk of hepatitis C virus re-infection ▶ Side effects: diabetes, obesity, osteoporosis
Thymoglobulin	<ul style="list-style-type: none"> ▶ Avoidance of renal toxicity ▶ Promotion of Treg expansion/tolerance 	<ul style="list-style-type: none"> ▶ Possible severe adverse reaction ▶ Must be used with added immunosuppression/short-term use
Interleukin 2 receptor antibody	<ul style="list-style-type: none"> ▶ Avoidance of renal toxicity 	<ul style="list-style-type: none"> ▶ Must be used with added immunosuppression/short-term use
Alemtuzumab	<ul style="list-style-type: none"> ▶ Specific effect on activated T cells ▶ Avoidance of renal toxicity ▶ Potential for re-setting the immune system ▶ Depletes cells from blood and lymph nodes 	<ul style="list-style-type: none"> ▶ Possible interference with tolerance induction? ▶ Must be used with added immunosuppression/short-term use ▶ Long-term effects of depletion still unknown
Belatacept	<ul style="list-style-type: none"> ▶ Avoidance of renal toxicity ▶ Need to administer only once a month 	<ul style="list-style-type: none"> ▶ Must be used with added immunosuppression ▶ Effects in recipients of liver transplantation are unknown

İmmünesupresiflerin olumlu/olumsuz etkileri

Agent	Attributes	Negatives/unknowns
Steroids	<ul style="list-style-type: none"> ▶ Broad spectrum of effects ▶ Reverses refractory acute rejection 	<ul style="list-style-type: none"> ▶ Risk of hepatitis C virus re-infection ▶ Side effects: diabetes, obesity, osteoporosis
Thymoglobulin	<ul style="list-style-type: none"> ▶ Avoidance of renal toxicity ▶ Promotion of Treg expansion/tolerance 	<ul style="list-style-type: none"> ▶ Possible severe adverse reaction ▶ Must be used with added immunosuppression/short-term use
Interleukin 2 receptor antibody	<ul style="list-style-type: none"> ▶ Avoidance of renal toxicity ▶ Specific effect on activated T cells 	<ul style="list-style-type: none"> ▶ Must be used with added immunosuppression/short-term use ▶ Possible interference with tolerance induction?
Alemtuzumab	<ul style="list-style-type: none"> ▶ Avoidance of renal toxicity ▶ Potential for re-setting the immune system ▶ Depletes cells from blood and lymph nodes 	<ul style="list-style-type: none"> ▶ Must be used with added immunosuppression/short-term use ▶ Long-term effects of depletion still unknown
Belatacept	<ul style="list-style-type: none"> ▶ Avoidance of renal toxicity ▶ Need to administer only once a month 	<ul style="list-style-type: none"> ▶ Must be used with added immunosuppression ▶ Effects in recipients of liver transplantation are unknown

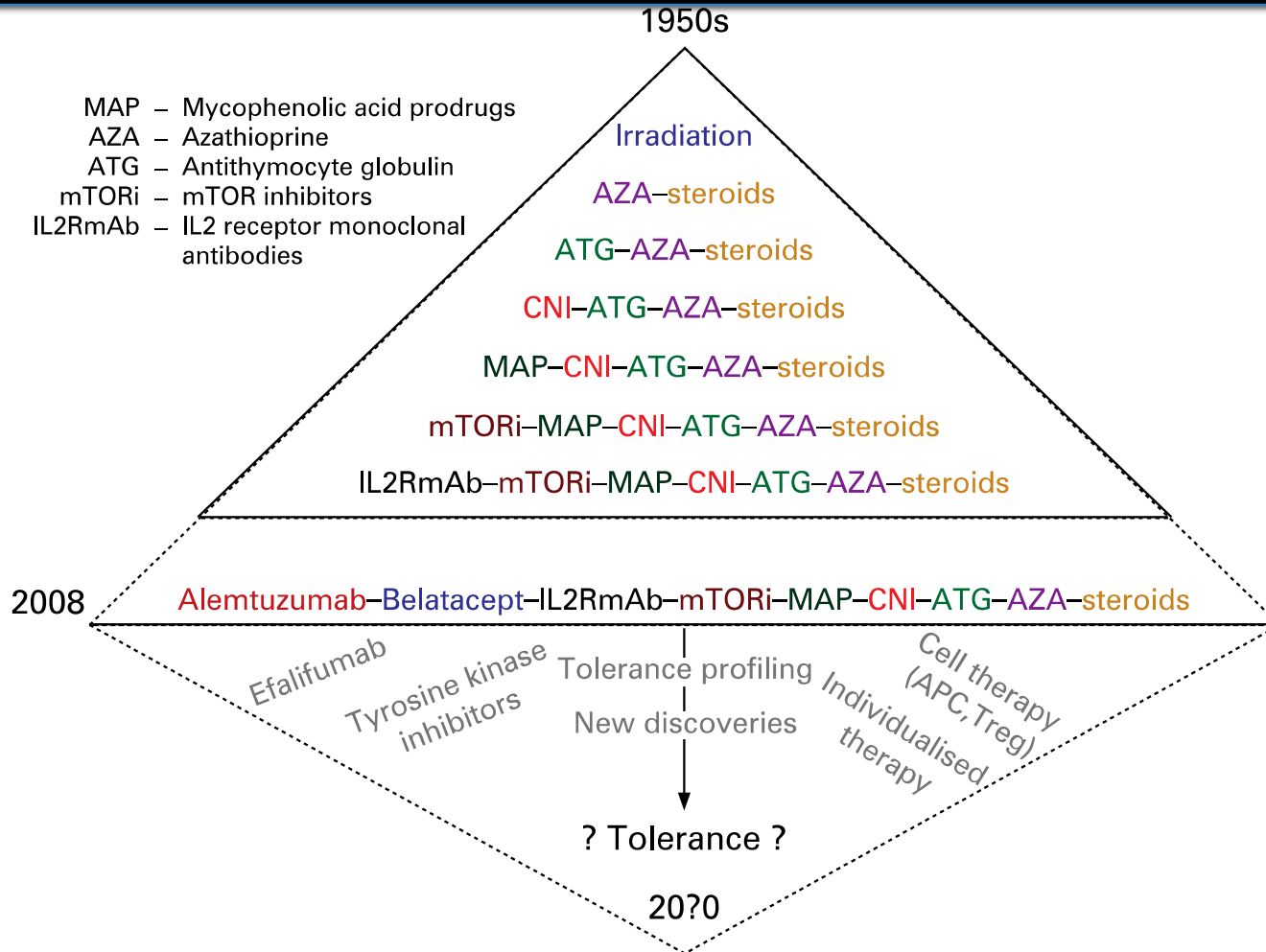
İmmünesupresiflerin olumlu/olumsuz etkileri

Agent	Attributes	Negatives/unknowns
Steroids	<ul style="list-style-type: none"> ▶ Broad spectrum of effects ▶ Reverses refractory acute rejection 	<ul style="list-style-type: none"> ▶ Risk of hepatitis C virus re-infection ▶ Side effects: diabetes, obesity, osteoporosis
Thymoglobulin	<ul style="list-style-type: none"> ▶ Avoidance of renal toxicity ▶ Promotion of Treg expansion/tolerance 	<ul style="list-style-type: none"> ▶ Possible severe adverse reaction ▶ Must be used with added immunosuppression/short-term use
Interleukin 2 receptor antibody	<ul style="list-style-type: none"> ▶ Avoidance of renal toxicity ▶ Specific effect on activated T cells 	<ul style="list-style-type: none"> ▶ Must be used with added immunosuppression/short-term use ▶ Possible interference with tolerance induction?
Alemtuzumab	<ul style="list-style-type: none"> ▶ Avoidance of renal toxicity ▶ Potential for re-setting the immune system ▶ Depletes cells from blood and lymph nodes 	<ul style="list-style-type: none"> ▶ Must be used with added immunosuppression/short-term use ▶ Long-term effects of depletion still unknown
Belatacept	<ul style="list-style-type: none"> ▶ Avoidance of renal toxicity ▶ Need to administer only once a month 	<ul style="list-style-type: none"> ▶ Must be used with added immunosuppression ▶ Effects in recipients of liver transplantation are unknown

İmmünesupresiflerin olumlu/olumsuz etkileri

Agent	Attributes	Negatives/unknowns
Steroids	<ul style="list-style-type: none"> ▶ Broad spectrum of effects ▶ Reverses refractory acute rejection 	<ul style="list-style-type: none"> ▶ Risk of hepatitis C virus re-infection ▶ Side effects: diabetes, obesity, osteoporosis
Thymoglobulin	<ul style="list-style-type: none"> ▶ Avoidance of renal toxicity ▶ Promotion of Treg expansion/tolerance 	<ul style="list-style-type: none"> ▶ Possible severe adverse reaction ▶ Must be used with added immunosuppression/short-term use
Interleukin 2 receptor antibody	<ul style="list-style-type: none"> ▶ Avoidance of renal toxicity 	<ul style="list-style-type: none"> ▶ Must be used with added immunosuppression/short-term use
Alemtuzumab	<ul style="list-style-type: none"> ▶ Specific effect on activated T cells ▶ Avoidance of renal toxicity ▶ Potential for re-setting the immune system ▶ Depletes cells from blood and lymph nodes 	<ul style="list-style-type: none"> ▶ Possible interference with tolerance induction? ▶ Must be used with added immunosuppression/short-term use ▶ Long-term effects of depletion still unknown
Belatacept	<ul style="list-style-type: none"> ▶ Avoidance of renal toxicity ▶ Need to administer only once a month 	<ul style="list-style-type: none"> ▶ Must be used with added immunosuppression ▶ Effects in recipients of liver transplantation are unknown

GEÇMİŞTEN BUGÜNE İMMUNSUPRESYON PROTOKOLLERİ



- MAP – Mycophenolic acid prodrugs
- AZA – Azathioprine
- ATG – Antithymocyte globulin
- mTORi – mTOR inhibitors
- IL2RmAb – IL2 receptor monoclonal antibodies

İdame immunsupresyon protokolleri

- Standart immunsupresyon

Steroid + Kalsinörin inhibitörü

- Böbrek koruyucu protokoller

Steroid + Düşük doz kalsinörin inhibitörü + Antiproliferatif/antimetabolit

- Steroidsiz protokoller

Antikor tdv ile indüksiyon + kalsinörin inhibitörü + antiproliferatif/antimetabolit

- Onkolojik hastalık varlığında immunsupresyon

Steroid + Düşük doz kalsinörin inhibitörü + Antiproliferatif/m-TOR inhibitörleri

İmmunosupresif tedavide riskler

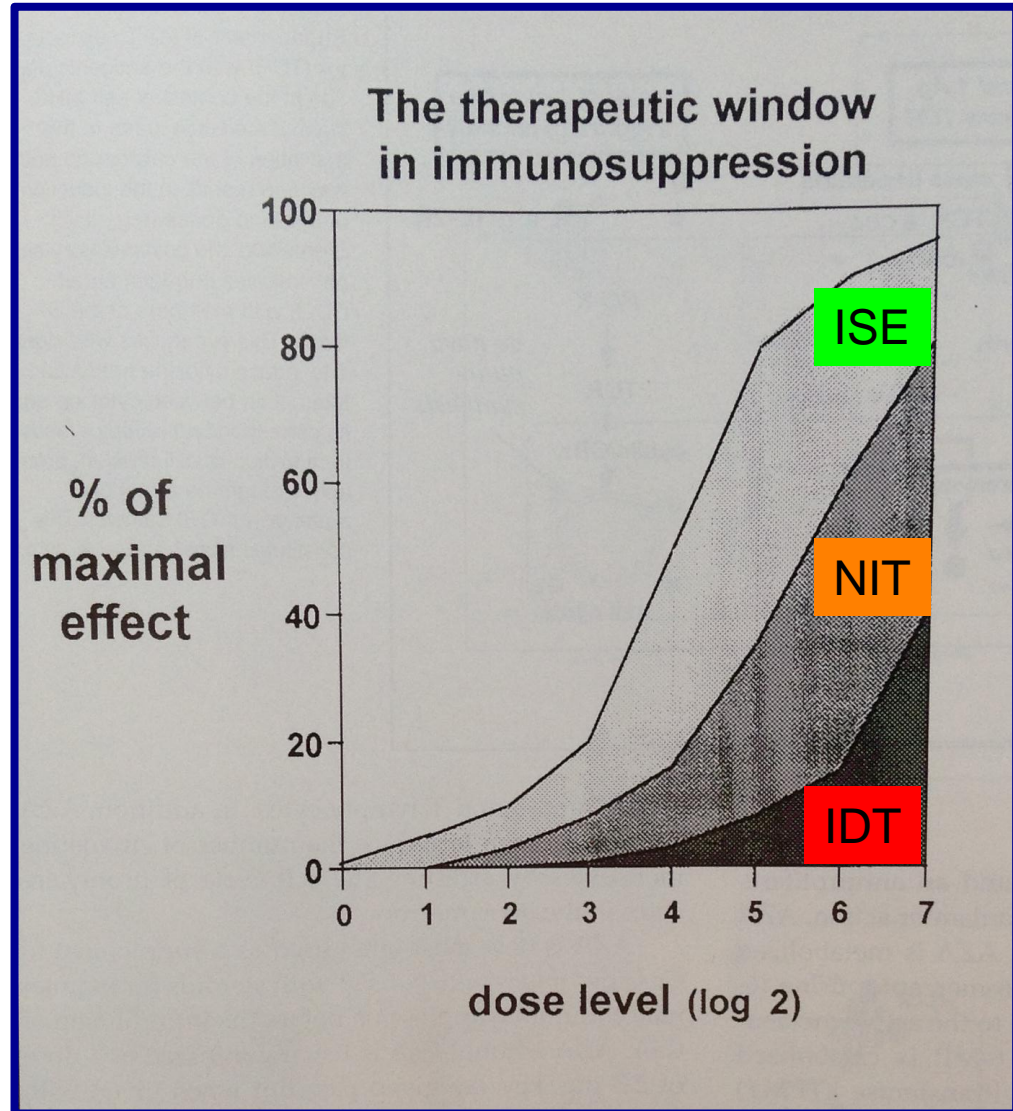
	Prednizon	Siklosporin	Takrolimus	Azatiopurin	MMF	Sirolimus
lökopeni				+	+	+
anemi				+	+	+
tromb ↓				+	+	+
nefrotok		+	+			
hipertans	+	+	+			
K ⁺ ↑		+	+			
Mg ↓		+	+			
Nörotoks	+	+	+			

İmmunosupresif tedavide riskler

	Prednizon	Siklosporin	Takrolimus	Azatiopurin	MMF	Sirolimus
Gastroint	+				+	
Pankreatit				+		
Hepatotok				+		
Hiperlipid	+	+	+			+
Glikoz ↑	+	+	+			
Jinjival hiperplazi		+				
Hirsutizm		+				

İmmünesupresif tedavi sırasında terapötik etki vs toksik etki

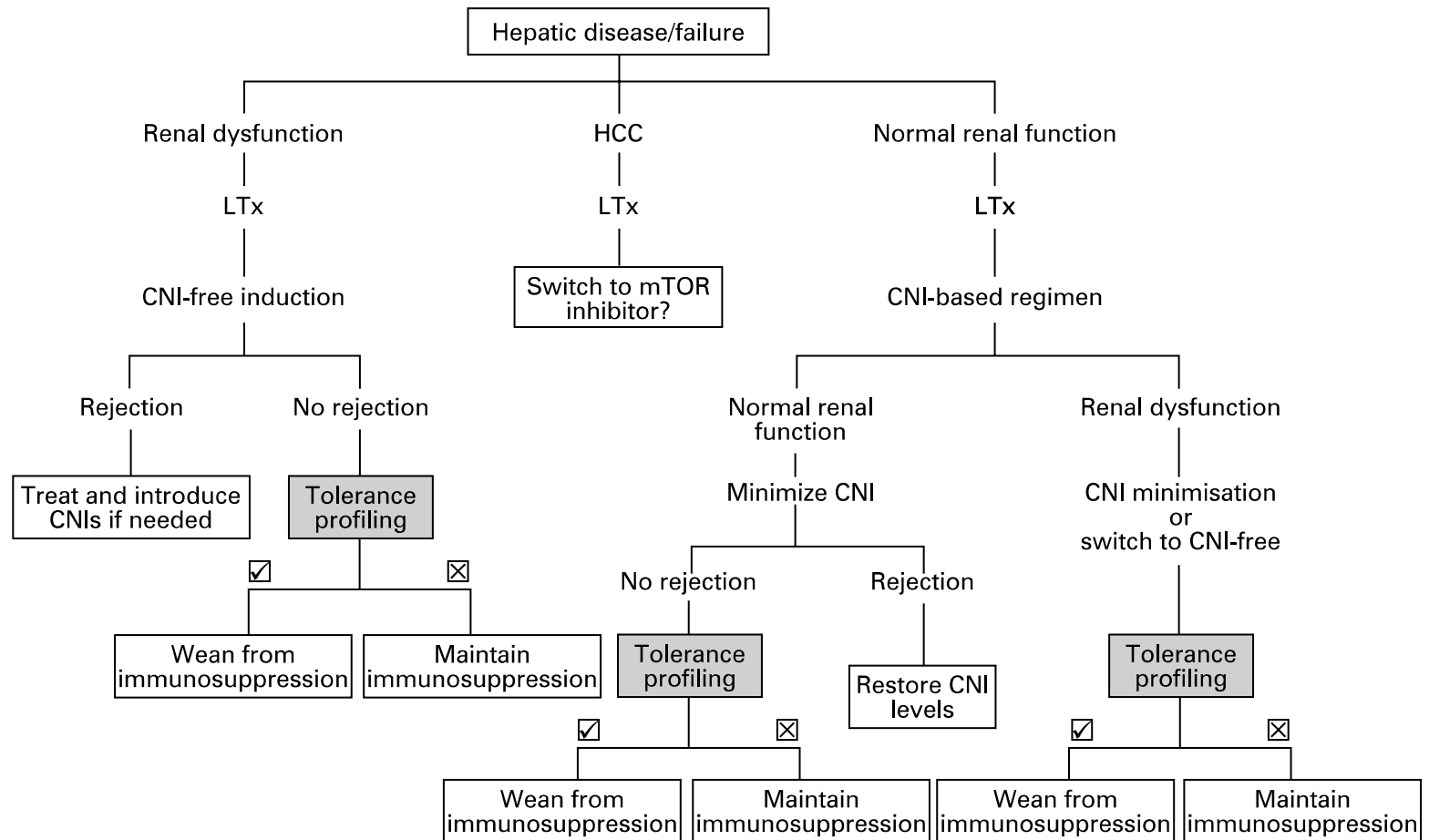
ISE: İmmünesupresif etki
NIT: Nonimmün toksisite
IDT: İmmünyetmezlik toksisitesi



İmmunsupresif tedavi sırasında immünyetmezlik / immundisregülasyon toksisitesi

- İnfeksiyon riskinde artış
- Fırsatçı infeksiyonlara eğilim
- Lenfoproliferatif hastalık
- Malign hastalık riski (lenfoma, kaposi sarkomu vs)
- Allerjik hastalık riskinde artış (eg. Besin allerjileri)

İmmunosupresif tedavinin minimalizasyonu





*Dikkatiniz için
teşekkürler*