Once Daily Tacrolimus

DR VILESH VALSALAN

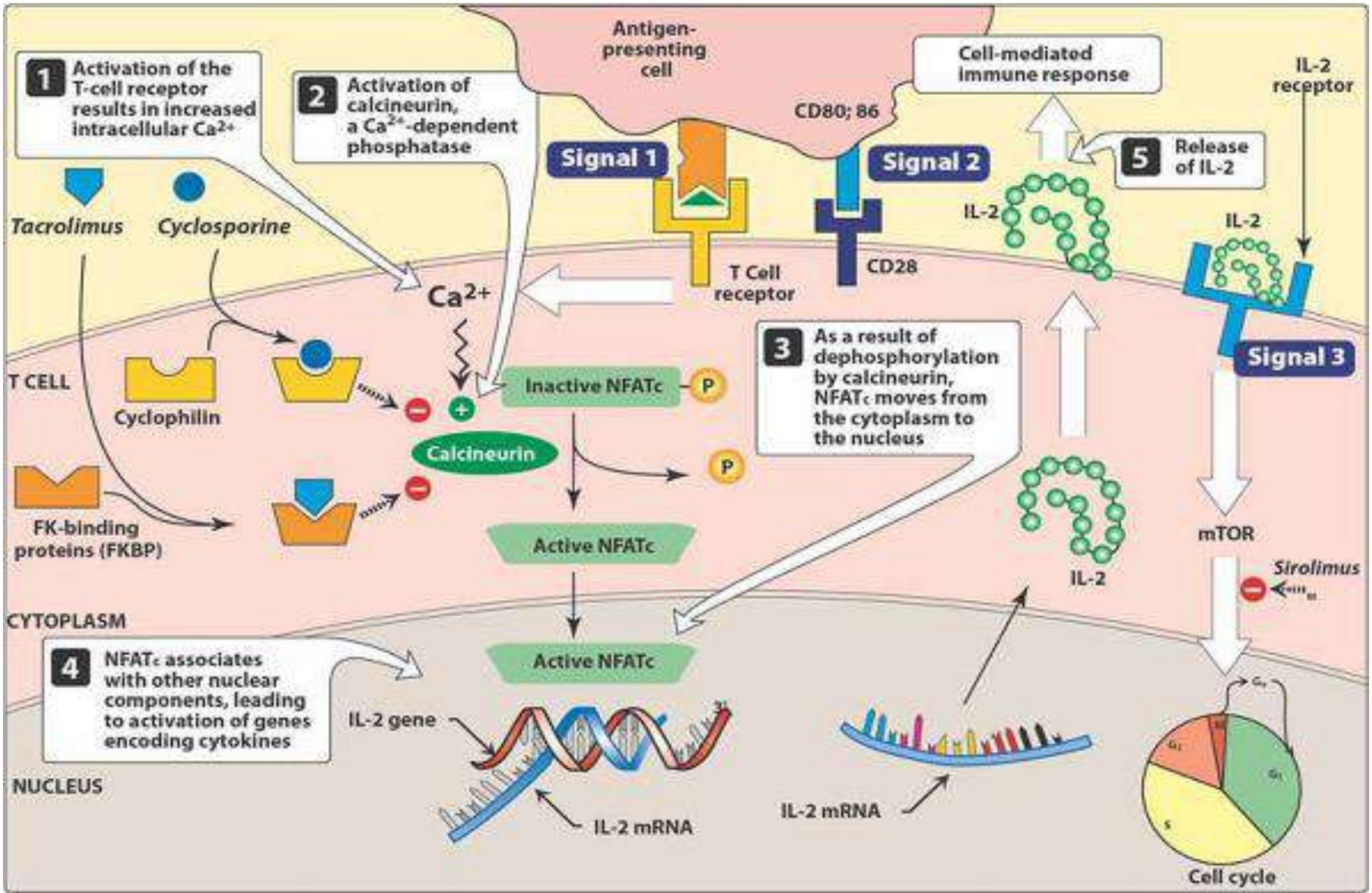
CONULTANT NEPHROLOGIST AND TRANSPLANT PHYSICIAN

ACADEMIC CORDINATOR - EXTRACORPOREAL NEPHROLOGY GROUP [ECNG]

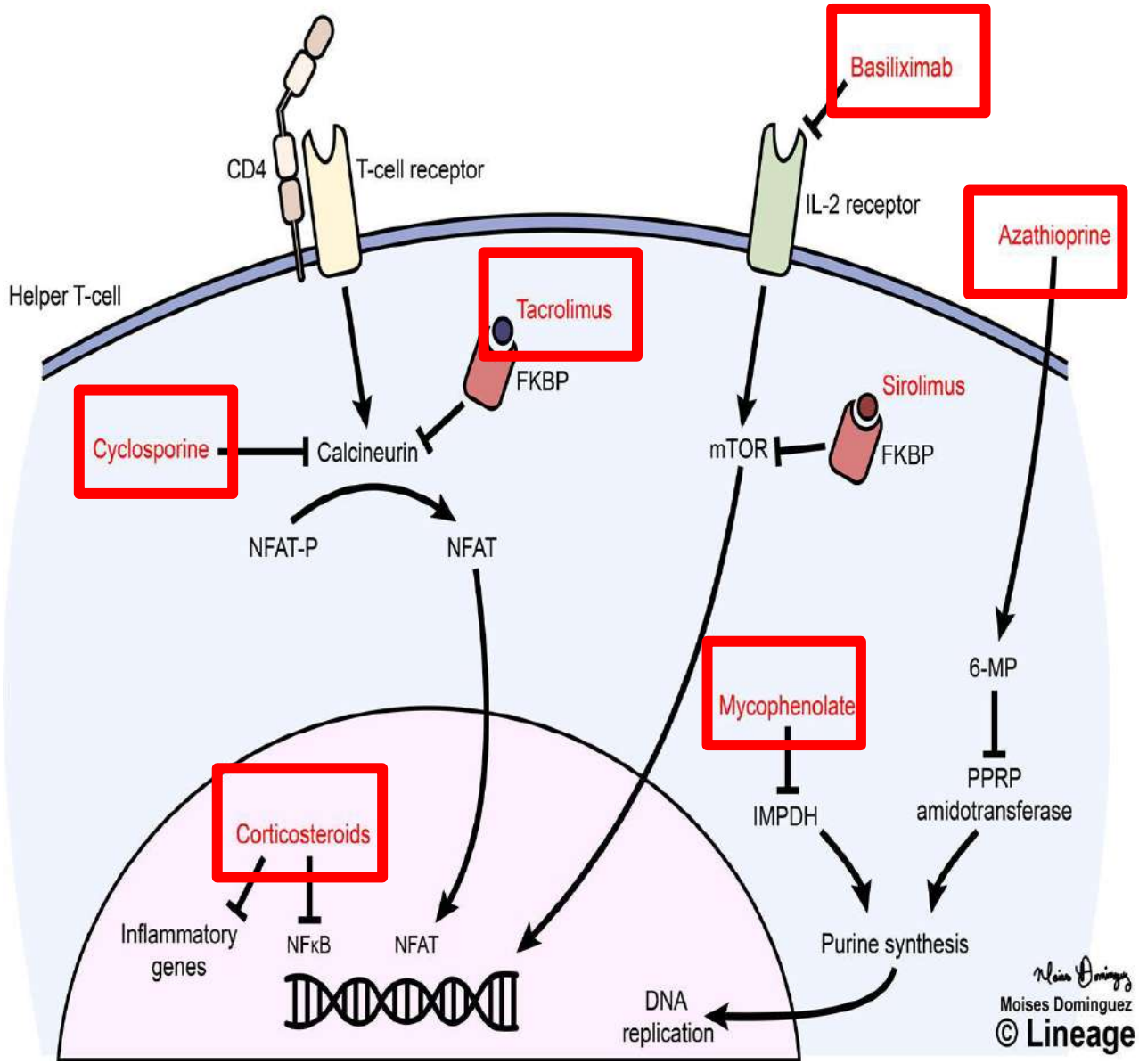
INTRODUCTION

- Once daily tacrolimus is designed to deliver the same 24-hour immunosuppressive effect with OD dosing and more stable exposure — but conversion requires brand-specific knowledge and close therapeutic drug monitoring.
- The pharmacokinetic differences between the two formulations come from the difference in excipients.
- Replacing croscarmellose by ethyl cellulose slows down the diffusion rate of tacrolimus, leading to a prolonged release.
- Tacrolimus OD compared to BD provides - lower intra patient variability , improved compliance , similar rates of patient survival, graft survival, renal function, and adverse effects.

Mechanism of action of CNIs



Targets of Select Immunosuppressants



Pharmacokinetics of Tacrolimus

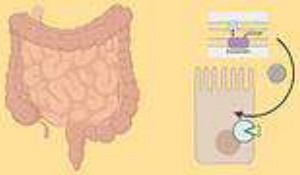
- The rate of absorption of tacrolimus is variable with peak blood or plasma concentrations being reached in 0.5 to 1 hours; approximately 25% of the oral dose is bioavailable.
- Tacrolimus is extensively bound to red blood cells, with a mean blood to plasma ratio of about 15; albumin and α_1-acid glycoprotein appear to primarily bind tacrolimus in plasma.
- Tacrolimus is completely metabolised prior to elimination.
- The mean disposition half-life is 12 hours and the total body clearance based on blood concentration is approximately 0.06 L/h/kg.
- The elimination of tacrolimus is decreased in the presence of liver impairment and in the presence of several drugs.

TACROLIMUS METABOLISM IN TRANSPLANTATION

- It is a potent immunosuppressant for solid organ transplantation
- Prevents organ rejection by inhibiting calcineurin
- **Challenge**: Narrow therapeutic window + high variability → Requires individualized dosing

ABSORPTION

Oral bioavailability: ~25% (range 5–93%)
Absorbed mainly in duodenum & jejunum
Poor water solubility
Presystemic metabolism: CYP3A4/ CYP3A5 in intestinal wall + P-glycoprotein efflux



DISTRIBUTION

Highly bound to erythrocytes & plasma proteins (~99%)

Crosses placenta, present in breast milk

METABOLISM

CYP3A isoenzymes in liver & intestine

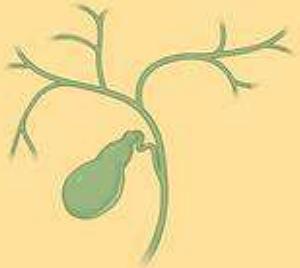
CYP3A4: Major enzyme in adults, high variability

CYP3A5: Polymorphic; expressers need higher doses

ELIMINATION

95% Biliary elimination

2.4% Urinary elimination



INTRINSIC FACTORS

Genetics: CYP3A5*1 ↑ clearance
Age: Kids need 2–4× dose
Race: African Americans → ↑ drug need
Liver: Dysfunction → ↓ clearance

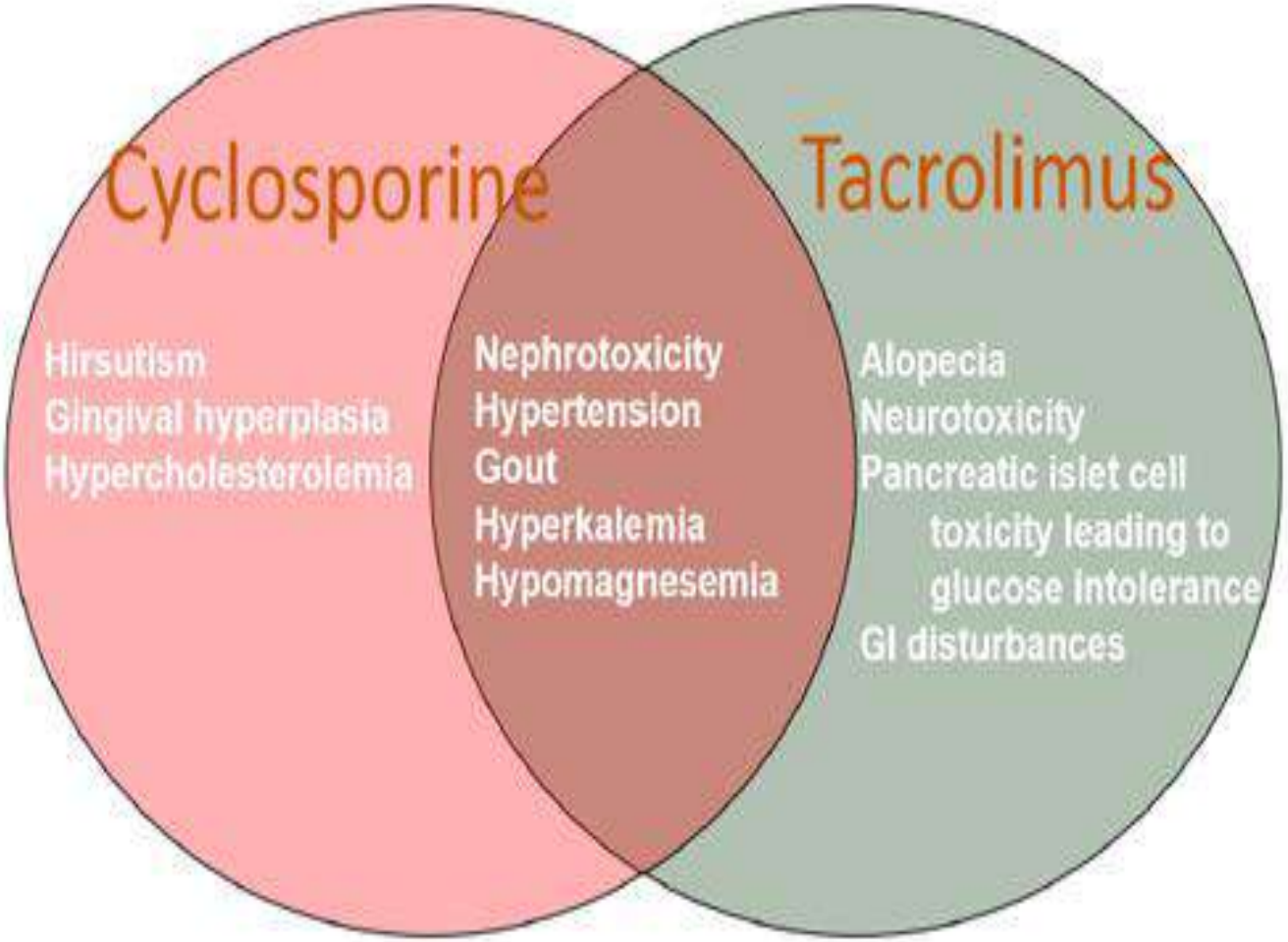
EXTRINSIC FACTORS

Drug interactions: CYP3A/P-gp
GI issues: Diarrhea → ↑ absorption
Food: Fatty meals → ↓ absorption
Steroids: High dose → ↑ metabolism

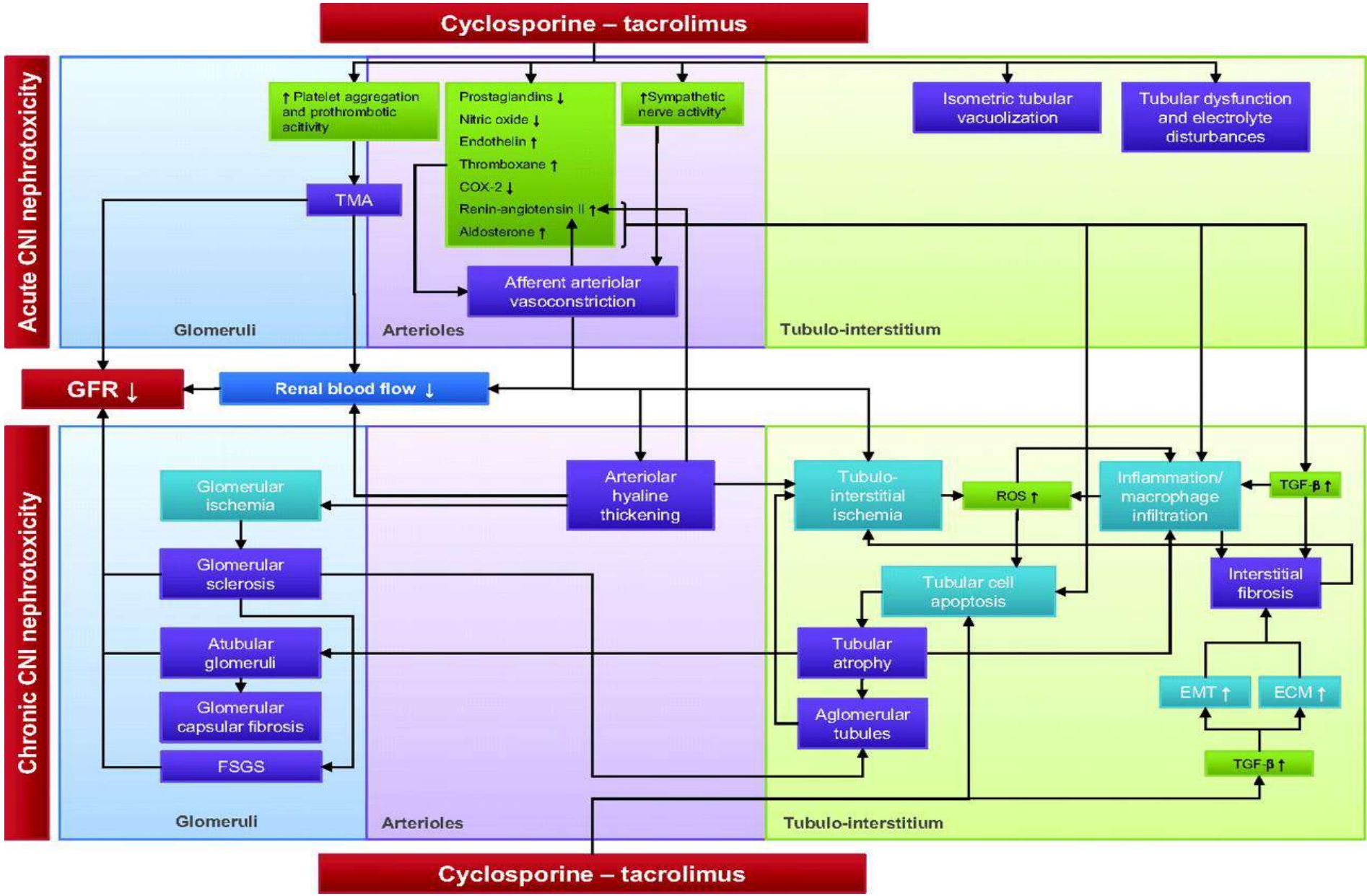
Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of tacrolimus in solid organ transplantation. *Clin Pharmacokinet.* 2004;43(10):623-653. doi:10.2165/00003088-200443100-00001

@roxnonna23

Issues with CNIs



CNI nephrotoxicity



GENES AND TACROLIMUS DOSING

- **1) CYP3A5 — primary determinant**
- Enzyme: metabolizes tacrolimus in liver & intestine
- Variants:
  - **CYP3A5*1 (expressor)** → *fast metabolism* → **needs higher doses**
  - **CYP3A5*3, *6, 7 (non-expressor)* → *slow metabolism* → **standard / lower doses**
- Common in many Asian and African populations; less common in Europeans.
- **Clinical impact:** CYP3A5 expressors often need ~1.5–2× higher starting dose (but always titrate to trough levels).

- **2) CYP3A4 — secondary contributor**
- Also metabolizes tacrolimus, especially when CYP3A5 is absent.
- Variants:
  - **CYP3A4*22** → ↓ activity → ↑ tacrolimus levels
  - **CYP3A4*1G** (common in Asians) → may ↑ clearance in some studies

GENES AND TACROLIMUS DOSING

- **3) ABCB1 (MDR1 / P-glycoprotein)**
- Affects absorption (gut) and distribution (kidney, brain).
- Polymorphisms (like **3435C>T**, **2677G>T/A**) may modestly influence dose needs and nephrotoxicity, but findings are inconsistent.

- **4) POR (P450 oxidoreductase)**
- Transfers electrons to CYP3A enzymes → influences activity.
- Some variants modify tacrolimus dose requirements (often subtle).

- **5) PXR (NR1I2 — Pregnane X Receptor)**
- Regulates CYP3A4/5 expression.
- Variants can change induction response (e.g., rifampicin, phenytoin).

- **6) CAR (NR1I3 — Constitutive Androstane Receptor)**
- Another regulator of CYP3A expression and induction.

Tacrolimus — BID → OD Conversion

Formulation Conversion Rules

Prograf® (IR, BID) → Advagraf® (OD)

- 1:1 total daily dose
- Monitor troughs and adjust
- Keep timing consistent vs meals

Prograf® / Advagraf® → Envarsus® XR (OD)

- Start ~70% of total daily dose
- Higher bioavailability
- Recheck levels within 3–5 days

- Dose to target trough + clinical context (do not rely on trough alone).
- CYP3A5 expressers may need higher OD doses.
- Avoid unsupervised formulation switching.
- Consider AUC in unstable/high-risk patients.

FEATURES	IR (Prograf)	Advagraf OD	Envarsus XR
Release	Fast	Slow	Very slow, distal
Absorption site	Proximal small bowel	Proximal → mid	Distal intestine
CYP3A exposure	High	Moderate–high	Lower
Bioavailability	Variable	Similar to IR	↑ Higher
Dose change	—	~1:1	↓ ~30%
Technology	Conventional capsule, rapid dissolution Absorbed mainly in the **proximal small intestine**	**Extended-release granules** inside the capsule Slower dissolution → prolonged absorption along intestine	LCPT / MeltDose Tacrolimus is micronized and dispersed on carriers → **dramatically increases surface area** Releases **distally** in the intestine (where there is less CYP3A) Slower, more controlled absorption