Limus is not limus– a proposal to adjust terminology in the context of drug-eluting stents

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Drug-eluting stents (DES) that elute sirolimus, everolimus, biolimus A9 or zotarolimus have been shown in numerous studies to efficiently inhibit restenosis after percutaneous coronary intervention (1). These drugs share a common mechanism of action: they inhibit mTOR, the mammalian target of rapamycin (mTOR). By doing so, they induce subsequent arrest during the early G_1 phase of the cell cycle (Fig. 1). This is distinct from the action of paclitaxel that inhibits cell division by interference with the spindle cell apparatus (2).

However, other drugs that end with "–limus" such as tacrolimus (3,4) and pimecrolimus (5,6) have been found to be ineffective for the prevention of restenosis in humans. Their name ending suggests that these drugs share a similar mode of action compared to the previously mentioned compounds, however, they work differently. Tacrolimus and pimecrolimus are calcineurin inhibitors (7), thus, they have anti-inflammatory properties but do not directly induce cell cycle inhibition in vascular smooth muscle cells that mainly comprise the cellular component of neointimal hyperplasia (8). Since restenosis is a proliferative disease, these drugs are inefficient to significantly reduce restenosis to the extent mTOR inhibitors do. Despite the marked difference in molecular drug mechanism that extends to a divergent clinical outcome, the term "limus-drugs" can be regarded as very common in the terminology of contemporary interventional cardiology (9-11).

Thus, we do suggest abandoning the misleading term "limus-drugs" but instead to use the terms mTOR inhibitors or calcineurin inhibitors, respectively (Table 1). This will alleviate the correct classification of drugs that – in terms of molecular action – merely share the ending of their name but have very different clinical outcomes when used on DES.

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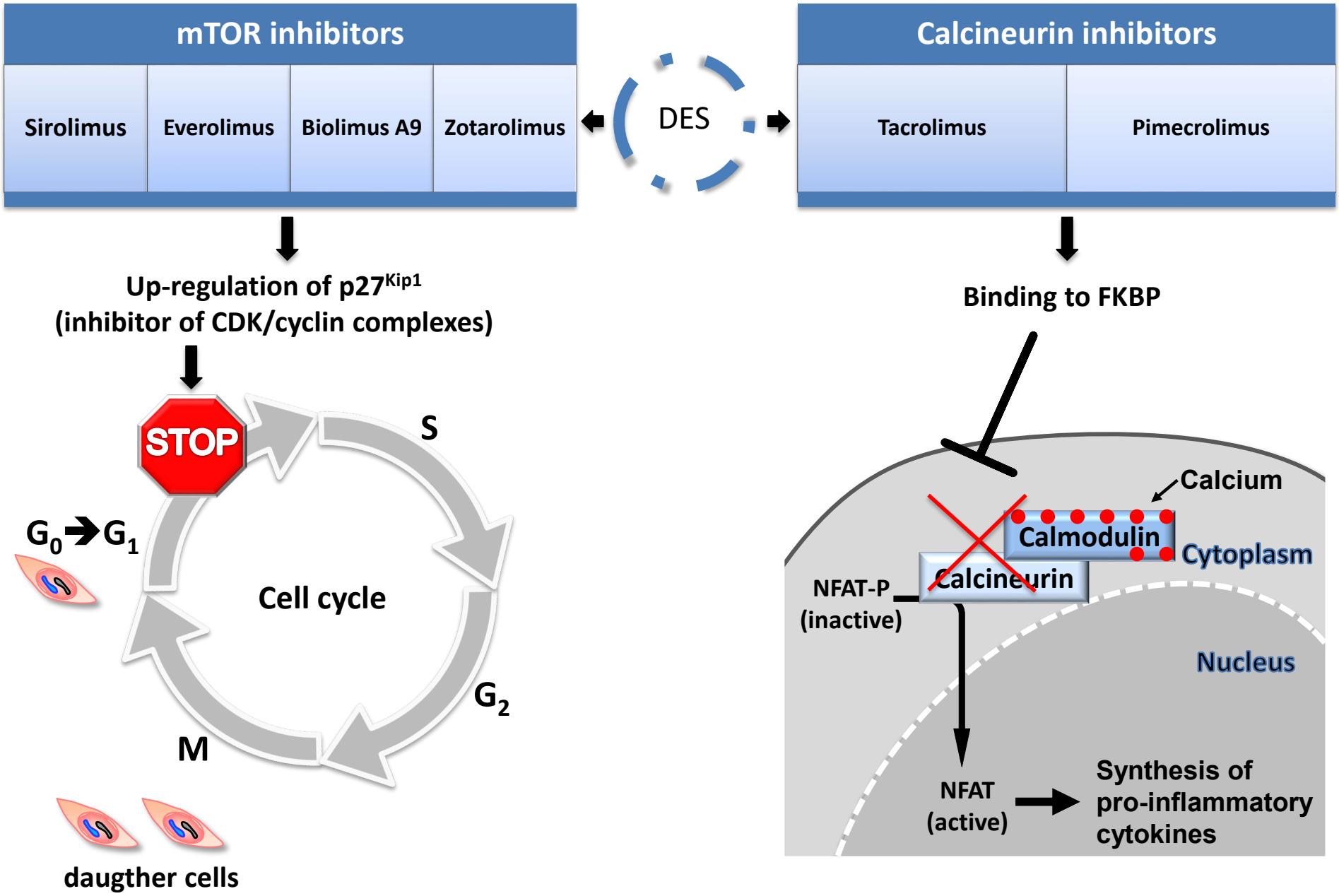
Table 1: Promiment members of the class of mTOR and calcineurin inhibitors that share the term "limus" and are or were used on DES platforms.

Compounds used on drug-eluting stents ending with "-limus"			
mTOR inhibitors		**Calcineurin inhibitors**	
Compound	**Stent platform(s)**	**Compound**	**Stent platform(s)**
Sirolimus	Cypher Cypher Select	Pimecrolimus	Corio, ProGenic
Everolimus	Xience V Xience Prime Promus Promus Element	Tacrolimus	Janus
Zotarolimus	Endeavor Endeavor Resolute, Resolute Intergity		
Biolimus A9	Biomatrix Nobori		

Figure 1. **Mechanism of action of compounds ending with "-limus" used on drug-eluting stents.**

Compounds that end with "-limus" belonging to the mTOR (mammalian target of rapamycin) inhibitor group up-regulate the tumor suppressor $p27^{Kip1}$, which interacts with and inhibits CDK (cyclin-dependent kinase)/cyclin complexes located in the nucleus of the cell thus causing cell cycle arrest in the G_1-phase. Drugs ending with "-limus" that belong to the calcineurin inhibitor group such as tacrolimus (FK506) and pimecrolimus interact in the cytoplasm of the cell with the immunophilin FKBP (FK506-binding protein) and the complex inhibits calcineurin. This inhibitory action of tacrolimus and pimecrolimus prevents calcineurin-dependent dephosphorylation and thus activation of the transcription factor NFAT (nuclear factor of activated T-cells), its nuclear import and the synthesis of NFAT-dependent pro-inflammatory cytokines.

Figure 1


mTOR inhibitors
Sirolimus
Everolimus
Biolimus A9
Zotarolimus
DES
Calcineurin inhibitors
Tacrolimus
Pimecrolimus
Up-regulation of p27Kip1
(inhibitor of CDK/cyclin complexes)
STOP
S
G0 → G1
Cell cycle
G2
M
daugther cells
Binding to FKBP
Calcium
Calmodulin
Cytoplasm
Calcineurin
NFAT-P
(inactive)
Nucleus
NFAT
(active)
Synthesis of
pro-inflammatory
cytokines