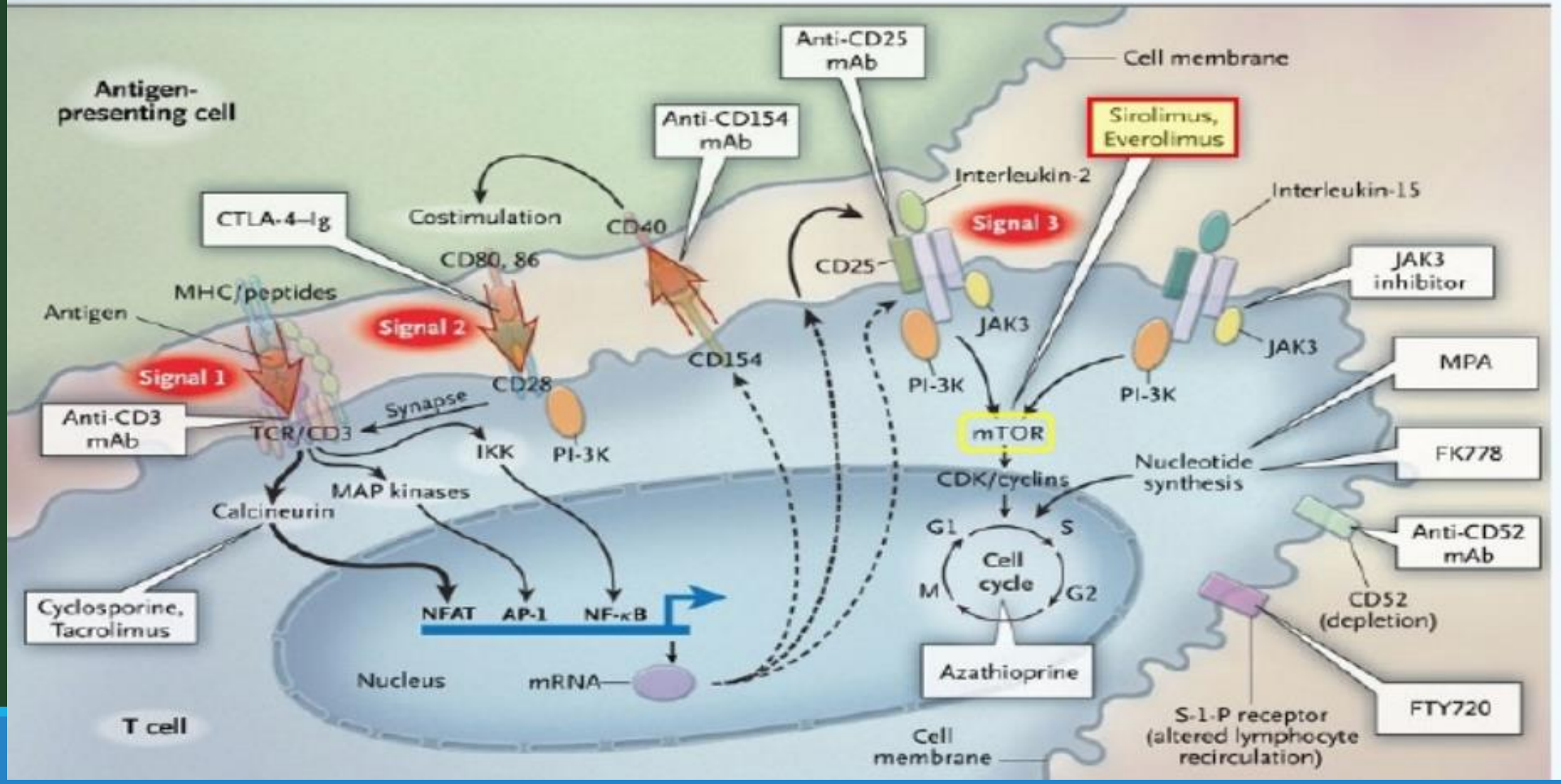
بسم الله الرحمن الرحيم

Anti Viral Effects of mTOR inhibitors

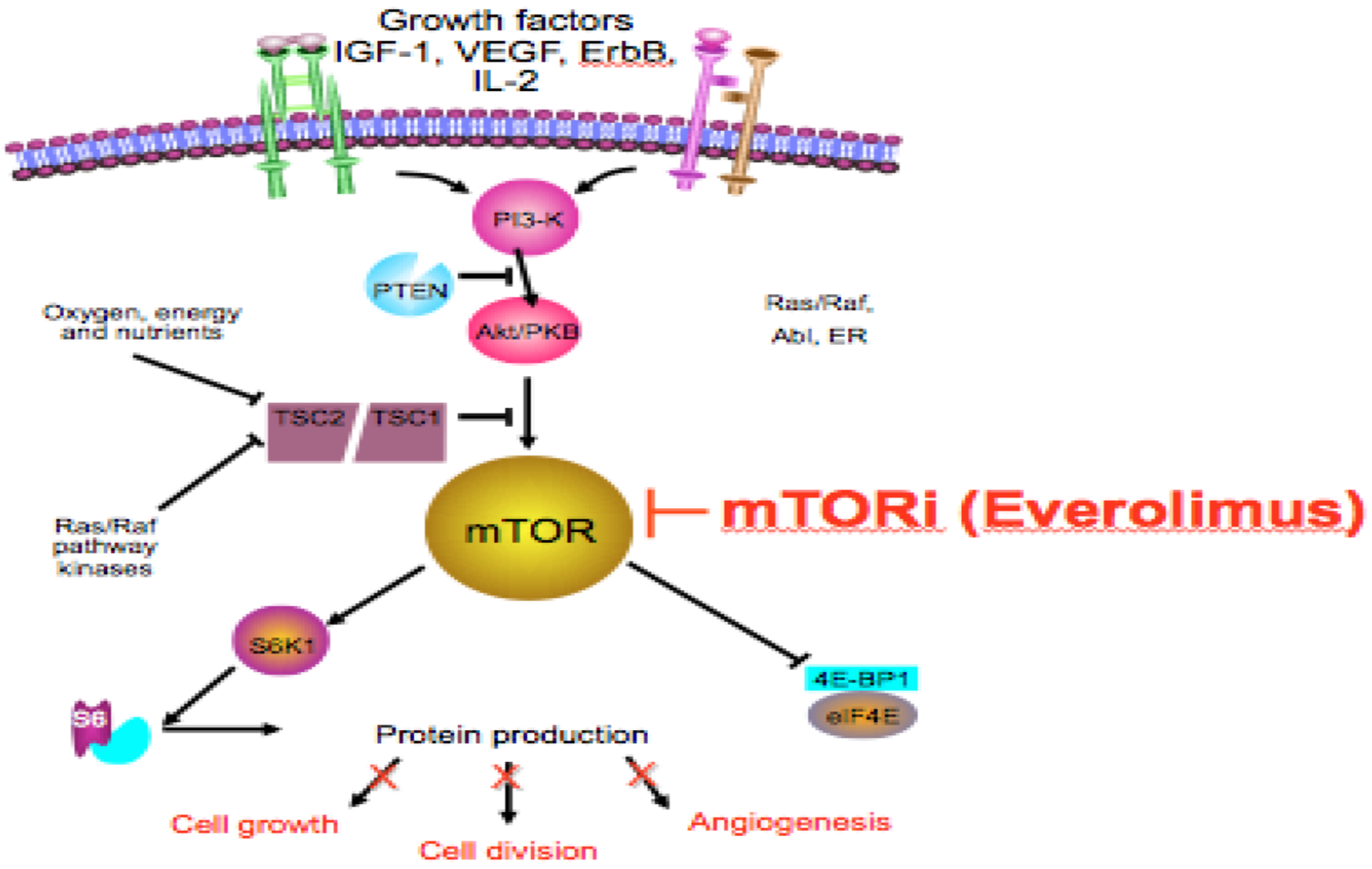
F POURREZAGHOLI
LABBAFINEJAD HOSPITAL
SBMU

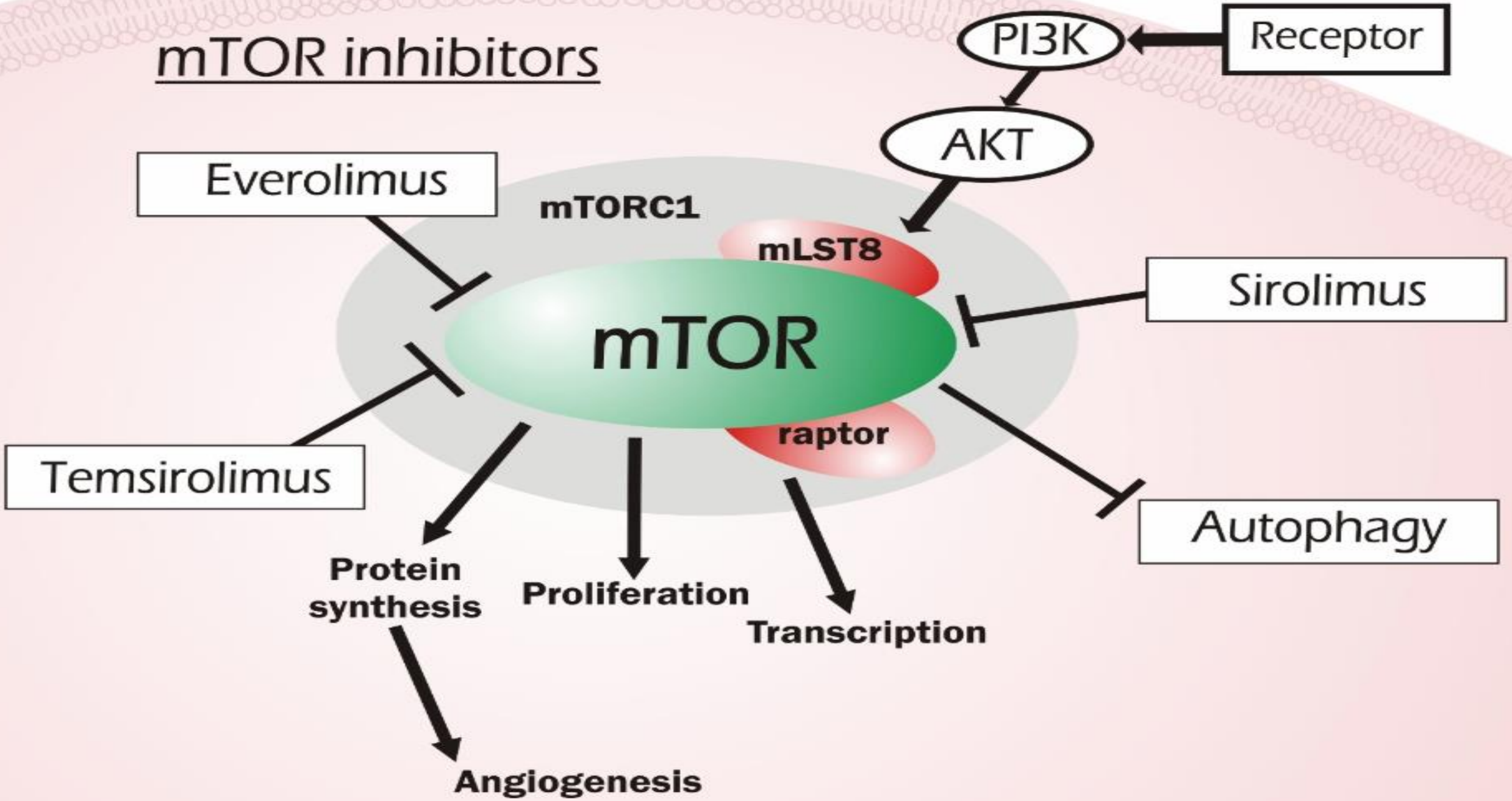
mTOR inhibitors and transplant

Three signal of T-cell activation



Antiproliferative effects of mTORi



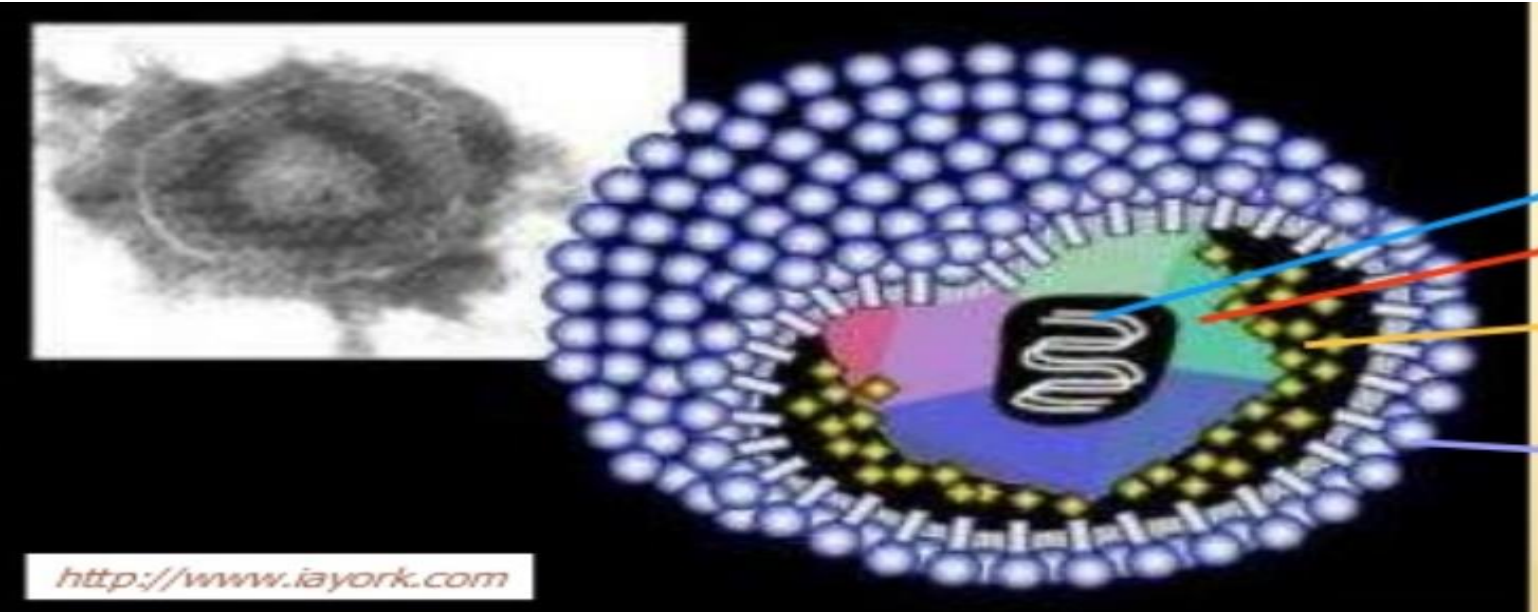

mTOR inhibitors
PI3K
Receptor
AKT
Everolimus
mTORC1
mLST8
mTOR
raptor
Sirolimus
Temsirolimus
Autophagy
Protein synthesis
Proliferation
Transcription
Angiogenesis

MECHANISM OF mTORi EFFECTS ON VIRAL INFECTIONS

The most prominent antiviral mechanism is likely the effect mTORis have on memory T cells

The mTORis increase the quality, and functionality and efficacy of memory T cells in response to vaccinations as well as viral stimuli

A significant increase in CMV)-specific CD8+ and CD4+ Tcells
mTOR inhibition is known to interfere with virus-mediated transcriptional events.



CMV Structure

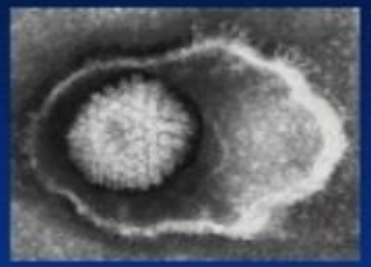
- Double-stranded DNA core
- Icosahedral nucleocapsid
- Tegument (proteinaceous matrix)
- Lipid bilayer envelope contains Glycoproteins

CMV is the most prominent viral infection after SOT

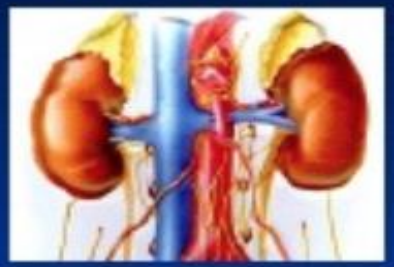
Emerging evidence suggests that mTORis exhibit a protective role against CMV reactivation and disease.

ANTILYMPHOCYTE ANTIBODIES

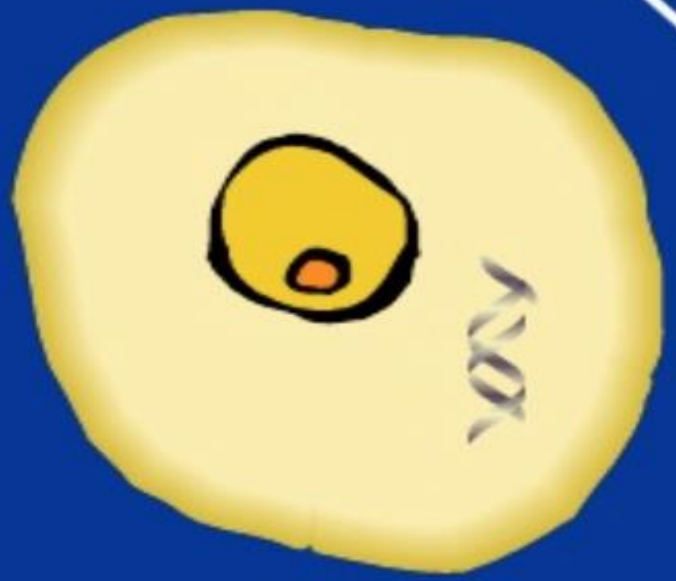
OTHER HERPES VIRUSES



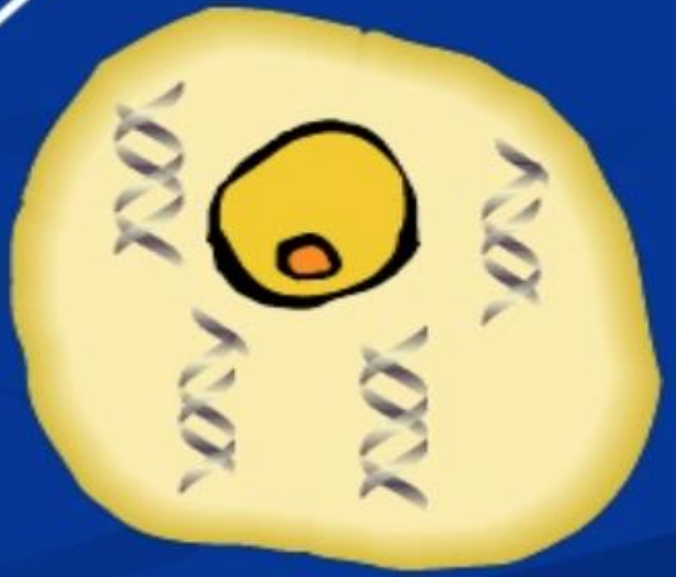
REJECTION



SEPSIS/ SURGERY



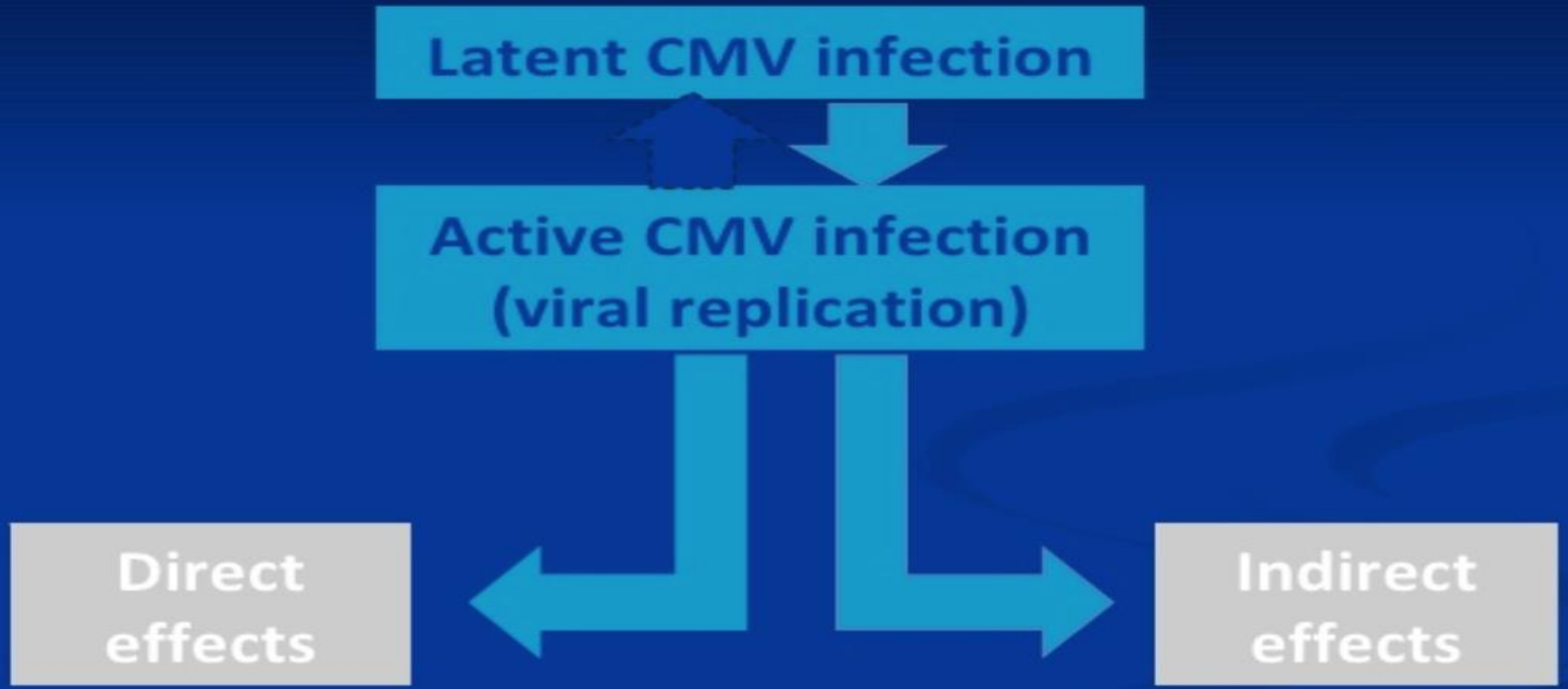
INFLAMMATION (CYTOKINES, NF-κB)



LATENT

CMV INFECTION

CMV Infection



Direct Effects of CMV Infection

CMV Viral Syndrome

- Fever, malaise, myalgias
- Leukopenia, thrombocytopenia, and other laboratory abnormalities

Tissue Invasive Disease

- Hepatitis
- Pneumonitis
- Colitis
- Carditis
- Nephritis
- Pancreatitis
- Retinitis

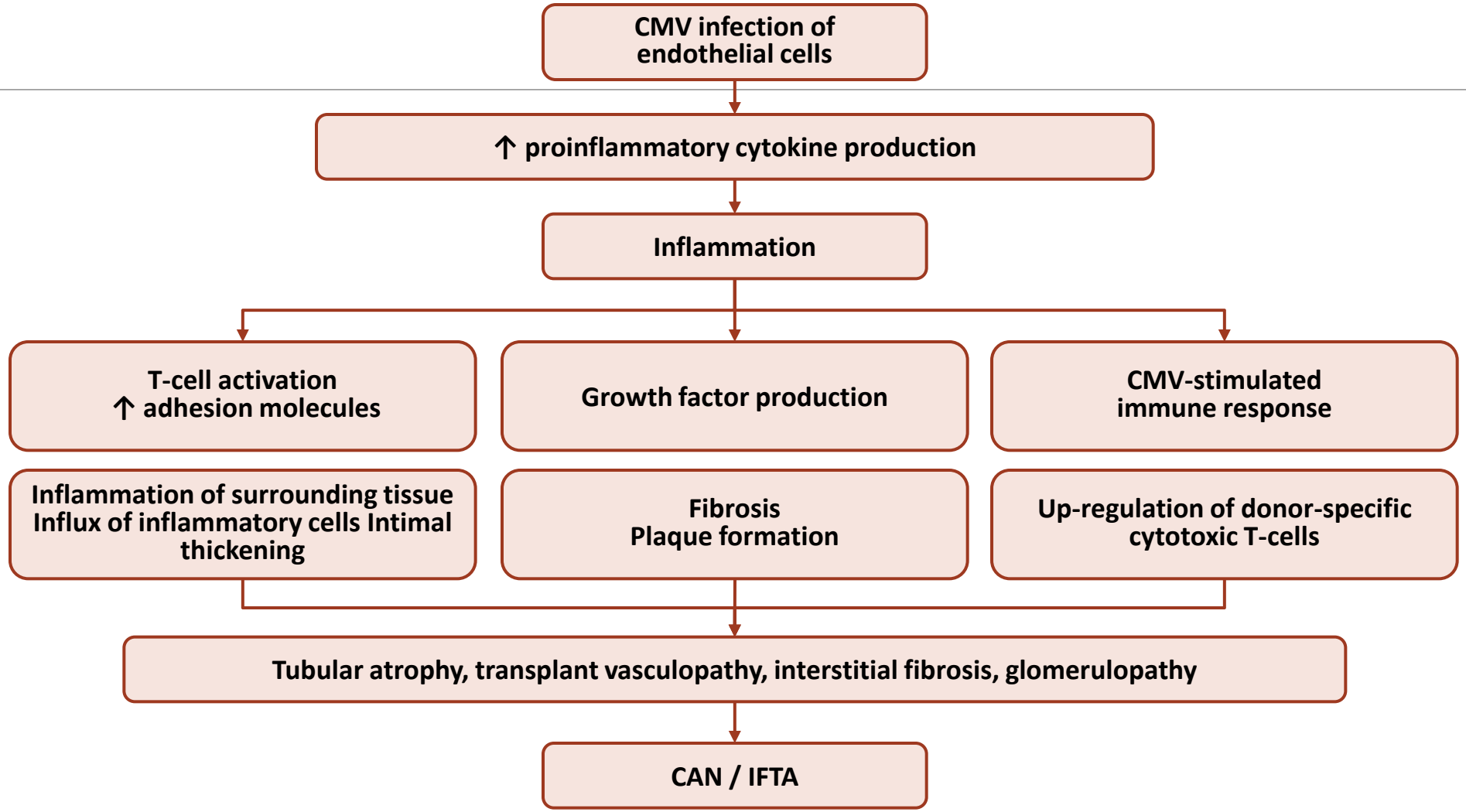
Indirect Effects of CMV Infection

Indirect Effects

Altered host immune response

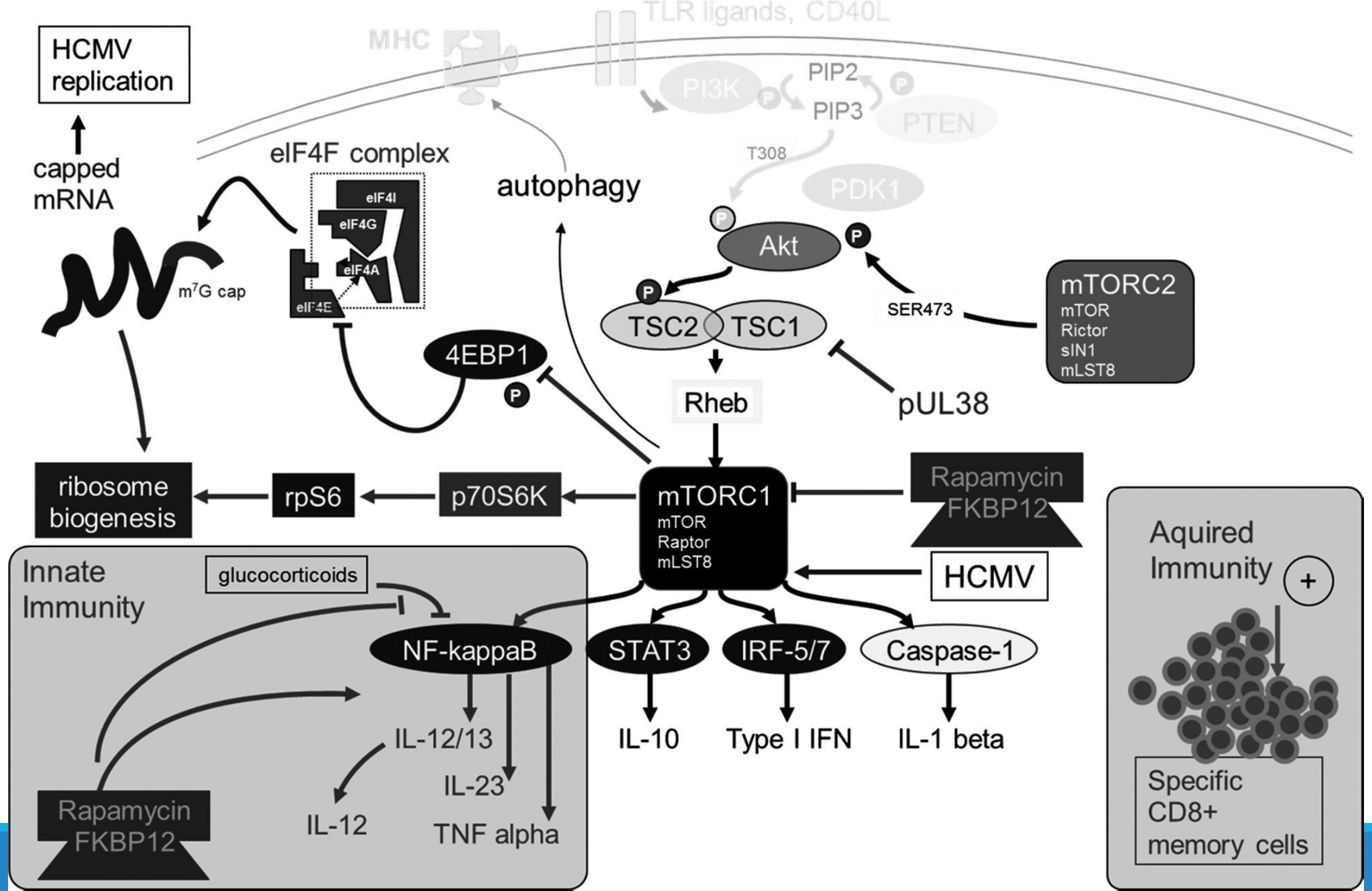
- Graft rejection; graft dysfunction
- Opportunistic infections: Bacterial fungal superinfection
- Decreased graft and patient survival
- Herpesvirus interactions: EBV/PTLD

CMV infection can lead to CAN / IFTA



CMV, cytomegalovirus; CAN, chronic allograft nephropathy; IFTA, interstitial fibrosis and tubular atrophy

Lautenschlager I *et al. Monogr Virol Basel, Karger* 2003;24:10–22


HCMV replication
capped mRNA
m7G cap
eIF4F complex
eIF4I
eIF4G
eIF4A
eIF4E
autophagy
MHC
TLR ligands, CD40L
PI3K
PIP2
PIP3
PTEN
T308
PDK1
Akt
SER473
mTORC2
mTOR
Rictor
sIN1
mLST8
TSC2
TSC1
4EBP1
Rheb
pUL38
ribosome biogenesis
rpS6
p70S6K
mTORC1
mTOR
Raptor
mLST8
Rapamycin FKBP12
HCMV
Innate Immunity
glucocorticoids
NF-kappaB
STAT3
IRF-5/7
Caspase-1
IL-12/13
IL-23
IL-12
TNF alpha
IL-10
Type I IFN
IL-1 beta
Rapamycin FKBP12
Aquired Immunity
+
Specific CD8+ memory cells

- *In vitro*, mTOR inhibitors increase the proliferation of gd T cells, which have the ability of eliminate CMV infected cells.
- CMV invasion occurs in part by inhibition of TH1-specific interferon-g–producing T cells, which are stimulated by mTOR inhibitors

In human macrophages, a sustained mTOR activation was shown to be mandatory for an efficient viral protein synthesis especially during the late phase of the viral cycle.

Treatment of these cells with an mTOR-I abrogated CMV replication.

The mTOR inhibitors may also stimulate innate immunity.

CMV specific CD4+ and CD8+ T cells are of particular importance for the immunologic response.

A percentage of Q0.03% CD4+ T-cells specific for the pp65 was predictive that patients would not develop CMV viremia .

Incidence of CMV is largely decreased in patients at risk receiving an mTOR inhibitor—usually in combination with a CNI.

Cases with **ganciclovir-resistant** CMV infection have been reported that were cured after switching to an mTOR inhibitor

Immunosuppressive treatment including an mTOR inhibitor might be the protocol of choice in patients with a high risk of CMV infection. The use of mTORi in high-risk patients (i.e., those who are D+R−) has been too sparse to recommend avoiding the use of CMV prophylaxis or preemptive.

CMV prophylaxis is needed in patients receiving an mTOR inhibitor who stop the drug or have an episode of acute rejection requiring treatment.

For (D^{+}/R^{-}) recipients CMV universal prophylaxis is probably advisable despite receiving mTORi.

Review

Transplantation 2018

The Role of mTOR Inhibitors in the Management of Viral Infections: A Review of Current Literature

The mTORis play a clear role in the management of **cytomega- lovirus**, and have data supporting their potential use for **BK virus** and **human herpesvirus 8–related Kaposi sarcoma**.

No data de- finitively supports mTORis for use in **Epstein-Barr virus**–mediated posttransplant lymphoproliferative disorder or **hepatitis C virus** viral replication

Summary of recommendations

Role in therapy	Conclusions	Quality of evidence to support conclusion
CMV		
mTORi for prevention of CMV	• De novo and early conversion to mTORi significantly reduces the risk of developing CMV. This risk reduction continues with or without the addition of a CNI. • More studies are needed before recommending the elimination of CMV prophylaxis without an appropriate preemptive approach in the setting of mTORi use.	High
Conversion to mTORi for treatment of CMV	• Data concerning the clearance of CMV with the use of mTORis is limited to case reports and therefore a conclusion cannot be made.	Low
BKV		
mTORi for prevention of BK	• De novo mTORi may reduce the incidence of BK viremia.	Moderate
Conversion to mTORi for treatment of BKV	• Conversion to an mTORi in patients with BKVAN may reduce BKV viral load and improve kidney allograft function. • Data concerning the clearance of BKV viremia in patients without BKVAN with the use of mTORis is limited and conflicting.	Low
HCV		
mTORi in HCV	• De novo mTORi or conversion to an mTORi may slow the progression of fibrosis in HCV patients. • mTORis do not appear to influence HCV viral loads.	Moderate
EBV		
mTORi for prevention of EBV-associated PTLD	• De novo mTORi use does not appear to have a role for the prevention of EBV-associated PTLD.	Low
Conversion to mTORi for treatment of EBV-associated PTLD	• There may be a survival benefit in transplant recipients with EBV-associated PTLD when converted to an mTORi compared with reduced/held immunosuppression.	Low
HHV8		
mTORi for treatment of HHV8-related KS	• mTORi appear to have benefit in the treatment of HHV8-associated KS	Moderate
HIV		
mTORi in HIV	• mTORi appear to reduce viral replication of HIV	Low

Two meta-analyses performed included 25 RCTs in which 10 200 transplant recipients were evaluated to assess differences in mTORi and CNI regimens on development of CMV.
Treatment with CNIs was associated with a combined estimated relative risk (RR) of 2.27 for CMV-related events.

Patients treated with a CNI alone, versus CNI/mTORi

combination, had a 2.45-fold risk for a CMV event.

The anti-CMV effect was statistically significant with an

mTORi regardless of de novo or conversion use; however, this effect in de novo and very early conversion to an mTORi was more pronounced compared with later conversion.

an 80% reduction in odds of experiencing CMV infection with everolimus compared with mycophenolate.
The anti-CMV effects of mTORis are evident with de novo use, early or
late conversion, in combination with a CNI, with or without CMV prophylaxis, and may also have benefit in the clearance of CMV.

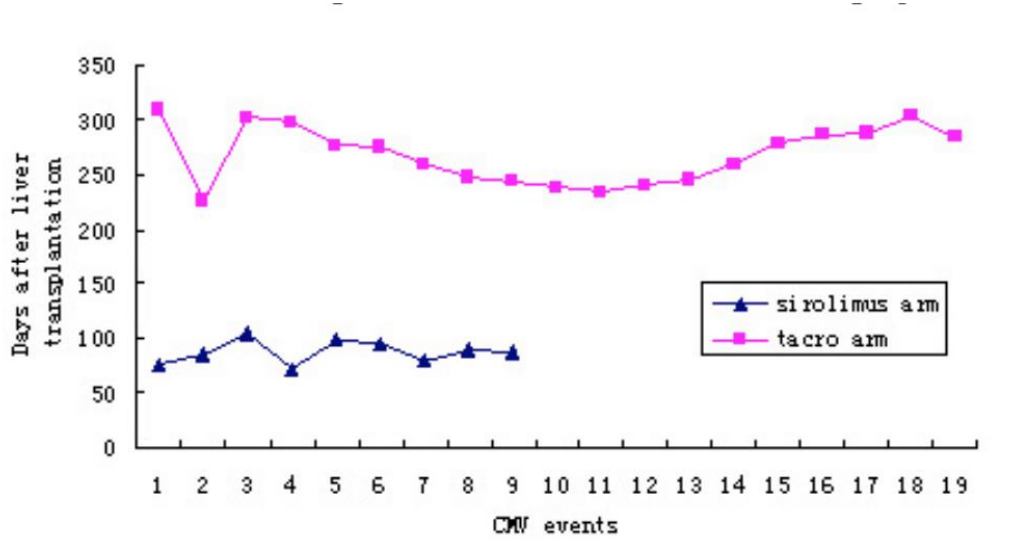
Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research

Original Article

The effect of sirolimus-based immunosuppression vs. conventional prophylaxis therapy on cytomegalovirus infection after liver transplantation

Conclusions

Sirolimus-based immunosuppression had a lower incidence of CMV infection compared with conventional prophylaxis therapy and did not increase rejection risks and mortality after liver transplantation, indicating that **with the use of an (mTOR)-inhibitor, CMV prophylaxis may be dispensable**.



The figure showed the incidence of CMV events between two groups after liver transplantation

- Analysis of large databases **(UNOS)** show that the mTORi (alone or associated with CNIs) reduce the CMV infection risk in kidney, heart, and lung transplantation

- This reduction is relevant both in seropositive and seronegative recipients.
- The relationship between mTORi use and CMV risk reduction in liver transplant recipients remains unclear.
- The use of mTORi is associated with a 30% reduction in the risk of polyomavirus-caused nephropathy.

THE USE OF mTORi IN PATIENTS WITH RECURRENT CMV INFECTION AFTER KIDNEY TRANSPLANTATION FREE

Ali Shendi, Kirtida Patel, Nadia Godigamuwe, Ben Caplin, Mark Harber

Volume 30, Issue suppl_3

May 2015

Conclusions:

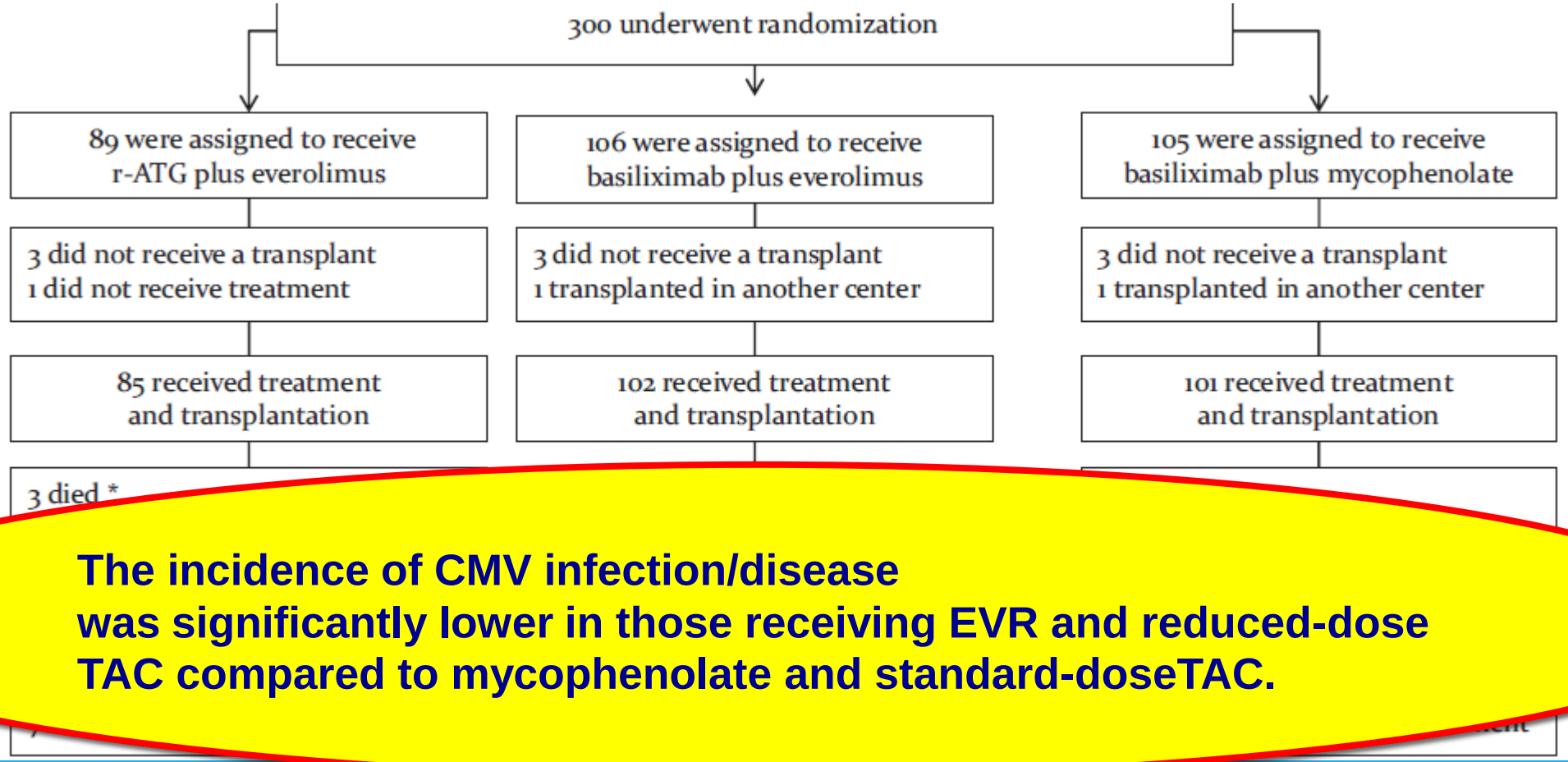
Patients with recurrent CMV viraemia who are high immunological risk patients or those with ganciclovir resistance represent challenging clinical problem

In our experience the use of an **mTORi,** often alongside tacrolimus, is a useful strategy in treating recurrent CMV viraemia without provoking rejection.

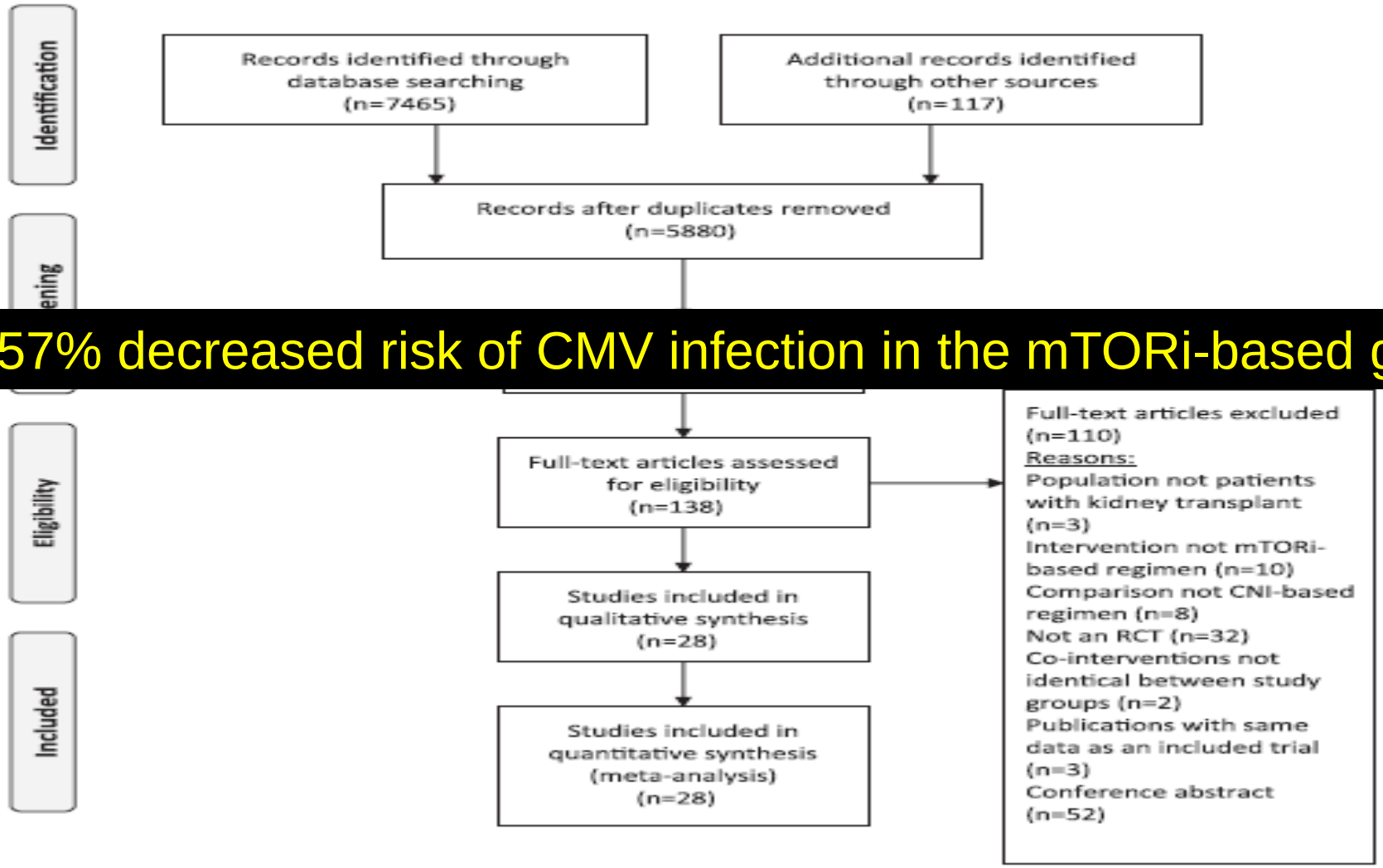
American Journal of Transplantation 2015; 15: 2655–2664
Wiley Periodicals Inc.

doi: 10.1111/ajt.13327

Reduced Incidence of Cytomegalovirus Infection in Kidney Transplant Recipients Receiving Everolimus and Reduced Tacrolimus Doses



The incidence of CMV infection/disease was significantly lower in those receiving EVR and reduced-dose TAC compared to mycophenolate and standard-doseTAC.



significant 57% decreased risk of CMV infection in the mTORi-based group

24 original studies with a total of 6211 participants.

Decreased Cytomegalovirus infection after antilymphocyte therapy in sirolimus-treated renal transplant patients

Kikumi S. Ozaki[a], Niels O.S. Câmara[a], Nelson Z. Galante[a], Luiz F.A. Camargo[b], Alvaro Pacheco-Silva[a,*]

[a]*Division of Nephrology, Universidade Federal de São Paulo, Rua Botucatu, 740, 04023-900, São Paulo, Brazil*
[b]*Division of Infectious Disease, Universidade Federal de São Paulo - Escola Paulista de Medicina, Hospital do Rim e Hipertensão, São Paulo, Brazil*

ELSEVIER

one prospective study of 1,470 renal transplant recipients (55 of whom were kidney– pancreas transplant recipients) found in multivariate analysis that the use of sirolimus had a protective effect against Cmv disease (odds ratio 0.27)

Organ	Question	Recommendations	Quality of evidence	Consistency of evidence
Kidney transplantation	Do mTOR inhibitors decrease the risk of CMV infection?	• The use de novo of an mTOR inhibitor, usually in combination with a calcineurin inhibitor reduces CMV infection and disease incidences to such extent that it may decrease the need for CMV universal prophylaxis. However, more studies would be necessary to support management without preemptive treatment strategies. • Immunosuppressive treatment including mTOR inhibitors (mTORi) might be the protocol of choice in patients with a high risk of CMV infection. • The use of mTORi in high-risk patients (i.e., those D^+R^-) has been very sparse to recommend avoiding the use of CMV prophylaxis or preemptive treatment strategies in these patients, so the standard prophylaxis or preemptive treatment with valganciclovir is advised. • Although CMV universal prophylaxis is usually prescribed in patients receiving ATG induction therapy, this prophylaxis may be omitted in patients receiving everolimus for primary immunosuppression. In these patients, avoidance of universal prophylaxis does not preclude the recommendation for a strategy of preemptive therapy. • In addition, CMV prophylaxis is needed in patients receiving an mTOR inhibitor who stop the drug or have an episode of acute rejection requiring treatment.	High	High

REVIEW

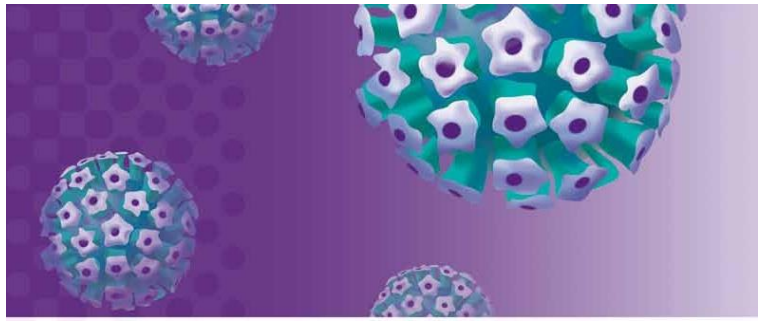
Role of mTOR inhibitors for the control of viral infection i solid organ transplant recipients

June 2016

- An mTOR-IY based immunosuppression, if started anyway, may be the tipping point toward the don’t use of a preemptive therapy.
- Especially,because the side-effect profile of (val-)ganciclovir and mTOR-I have some negative overlap on RBC and WBC counts.

BKV is a highly prevalent virus that can be reactivated in the transplant population

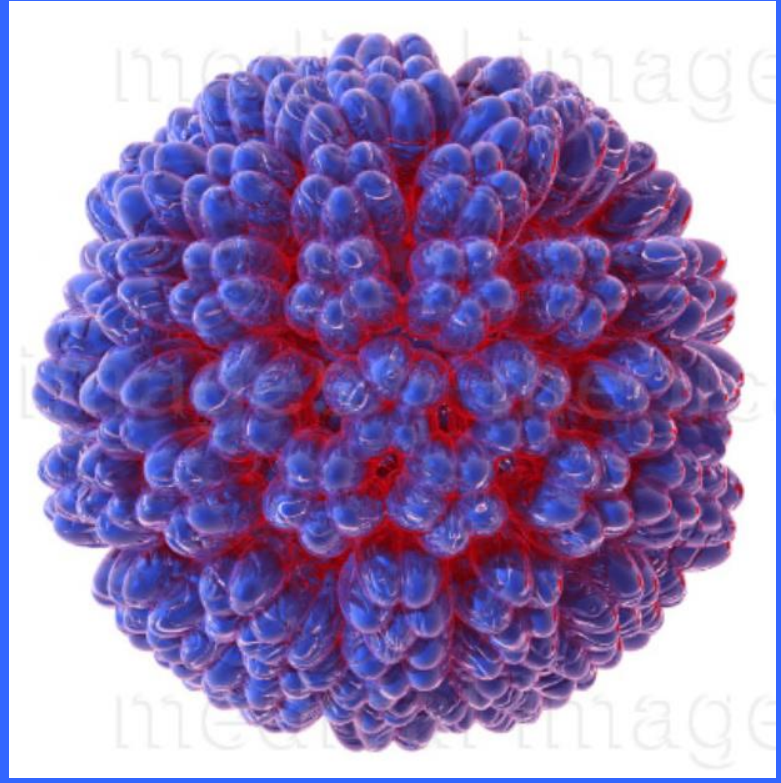
- BKV[1]
  - 1st detected in 1971 from the urine of a renal transplant patient, initials 'BK'
  - DNA virus, member of the polyoma virus family
- Highly prevalent
  - Almost 80% of the population is infected[1,2]
- Primary infection: subclinical or unspecific
  - Target tissues: uroepithelium, lymphoid tissue and brain[3]
- Latent infection
  - Mainly in the urinary tract[1]
  - Can remain latent for years or decades[4]
- BKV can be reactivated in the transplant population[1,4]



BKV, BK virus

1. Beimler J *et al. Nephrol Dial Transplant* 2007;22(Suppl 8):viii66–71; 2. Hirsch HH *et al. N Engl J Med* 2002;347:488–96;
3. Bohl DL, Brennan DC. *Clin J Am Soc Nephrol* 2007;2(Suppl 1):S36–46; 4. Randhawa P, Brennan DC. *Am J Transplant* 2006;6:2000–5

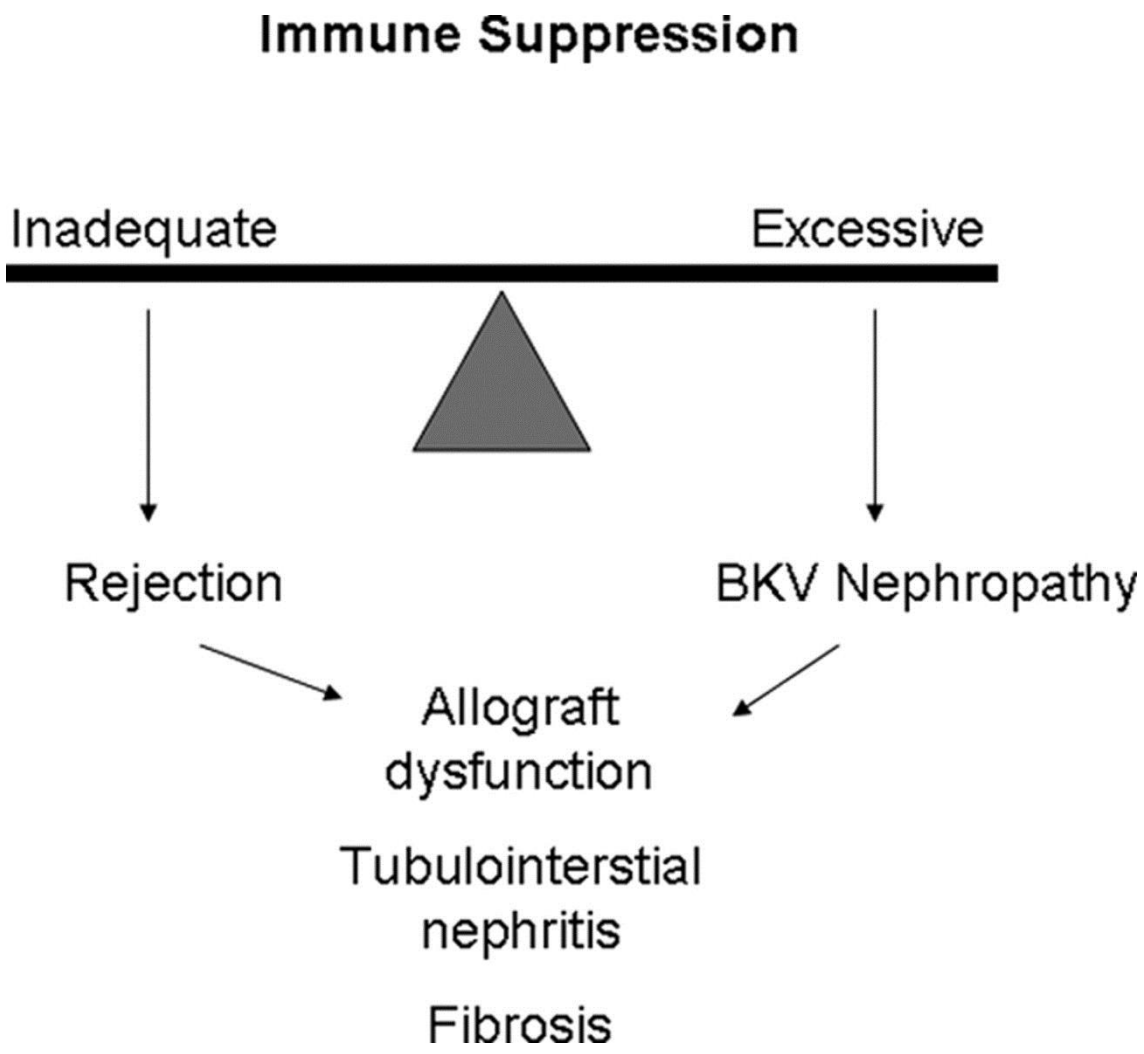
BK VIRUS



BK virus (BKV) is known to cause BKV-associated nephropathy (BKVAN) and is an important cause of graft loss in renal transplant recipients.

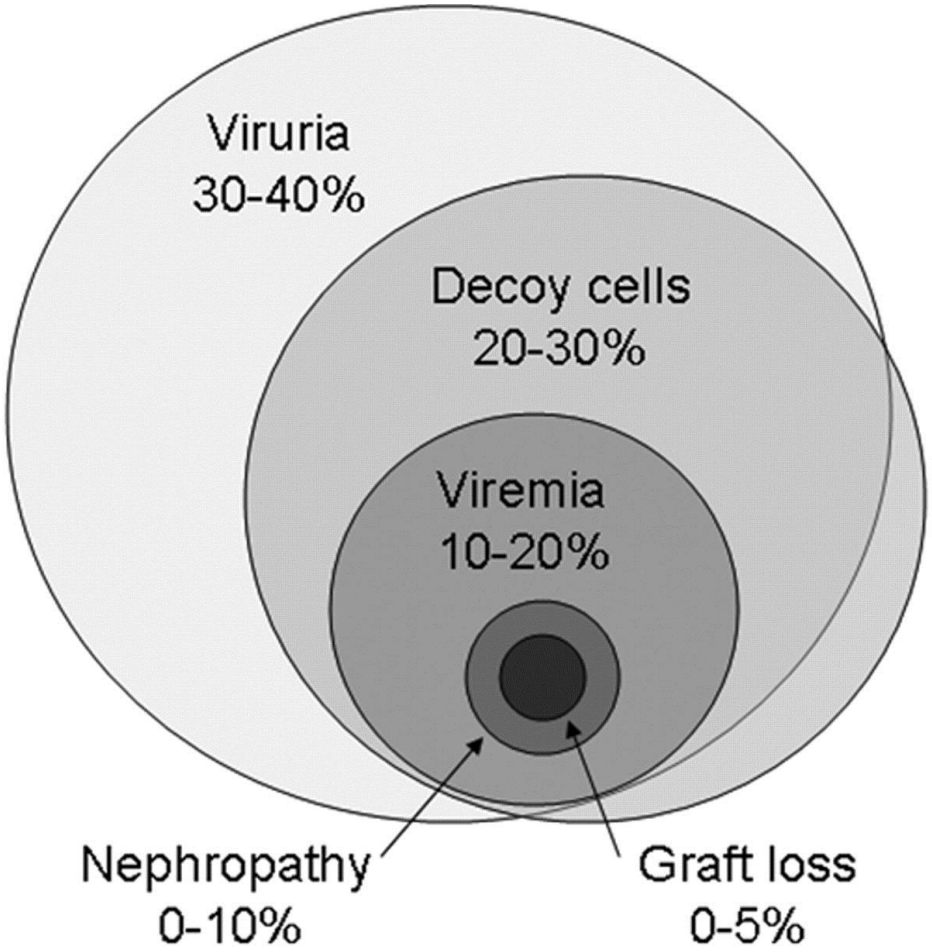
The level and quality of evidence supporting mTORis in the treatment and prevention of BKV post-SOT is poor and limited to renal transplantation.

Impaired immune suppression balance.



Bohl D L , Brennan D C CJASN 2007;2:S36-S46

Type and prevalence of BK virus (BKV) infections in kidney transplant recipients.



*Rare cases of nephropathy without viremia or viremia without viruria may occur

Bohl D L , Brennan D C CJASN 2007;2:S36-S46

BKV infection was significantly more prevalent within the first year post-transplant in TAC-treated patients compared to patients that received CsA

As a virus, BKV relies on the host's cellular machinery to replicate.

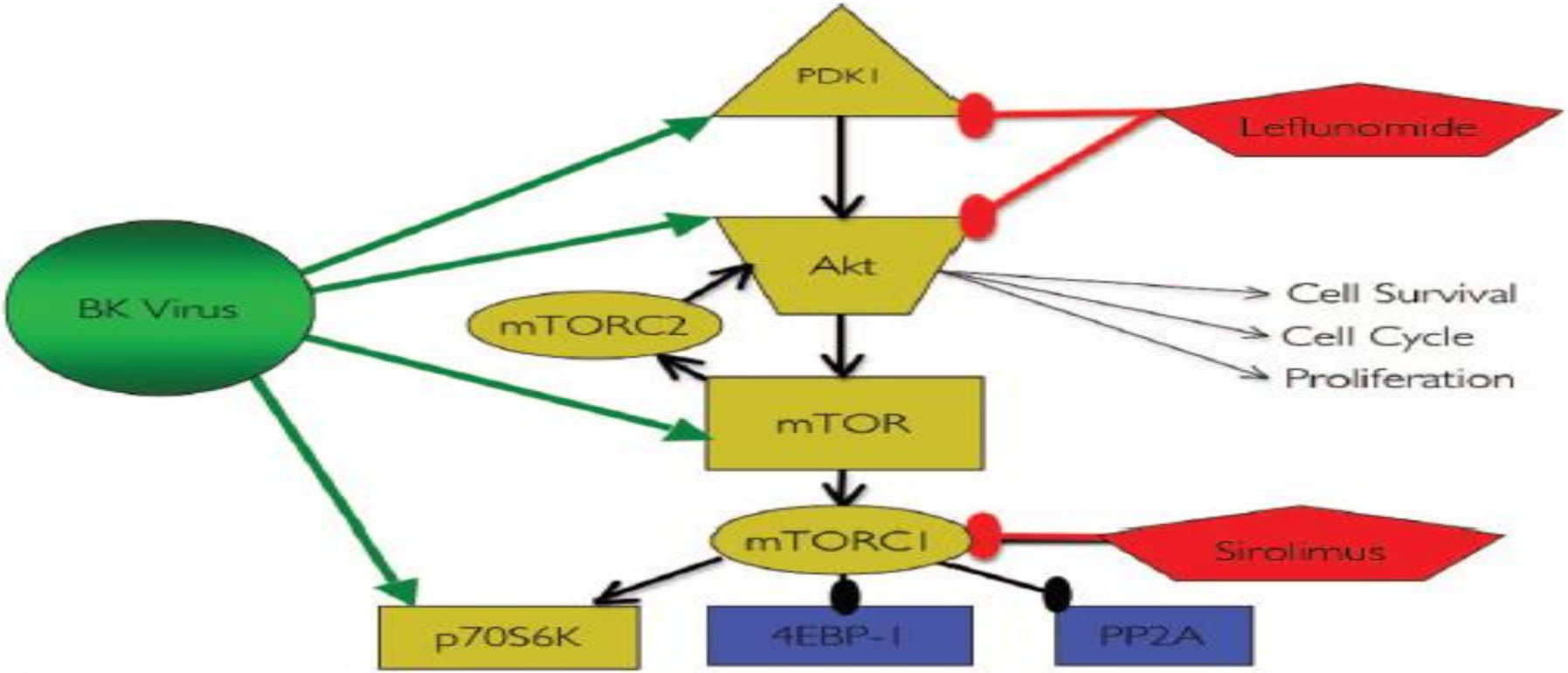
Upon entry into a cell, BKV induces cellular stress. This stress, down-regulates DNA replication and can then induce apoptosis or necrosis.

Progression of BKV infection to BKVAN leads to graft loss in up to 60% of affected patients

Anti-BK Virus Mechanisms of Sirolimus and Leflunomide Alone and in Combination: Toward a New Therapy for BK Virus Infection

CLINICAL AND TRANSLATIONAL RESEARCH

(*Transplantation* 2010)



Virus:
Protein Synthesis (T antigens, Protein Coat)
Cell Cycle (DNA Replication, host and virus)

Host Cell:
Protein Synthesis, Growth, Cell Cycle

The Akt/mTOR pathway showing the interactions of BK virus and kinase inhibitors, sirolimus, and leflunomide.
Growth factors and mitogens activate the Akt/mTOR pathway through PDK1 phosphorylation of Akt

Akt indirectly activates mTOR. mTOR exists in two protein complexes,mTOR complex 1 (mTORC1), which phosphorylates p70S6K and 4EBP-1 to initiate protein translation, and mTORC2 which can phosphorylate Akt on a different site than PDK1

This phosphorylation may activate Akt or change its substrate specificity. mTOR also inhibits PP2A,thereby reducing dephosphorylation of Akt.
Only mTORC1 is inhibited by sirolimus

BK virusinfection causes phosphorylation of PDK1, Akt, mTOR, and p70S6K.
Sirolimus inhibits p70S6K phosphorylation and BK large T antigen expression.
Leflunomide inhibits PDK1 and Akt phosphorylation and reduces BK virus DNA replication.

Place of mTOR inhibitors in management of BKV infection after kidney transplantation

Thomas Jouve[1,2], Lionel Rostaing[1,2,3,4*], Paolo Malvezzi[1]

J Nephropathol. 2016; 5(1): 1-7

BKV-specific T-cell responses, and particularly BKV-specific interferon (IFN)-γ–producing T-cells are markers of antiviral immune protection

BK antigen-specific expansion and not the overall T-cell activation was affected by mTORIs

In addition, SRL may be associated with lower incidence rate of BKVAN, even when combined with low-dose CNIs .

Article type : Original Article

Conversion from tacrolimus-mycophenolate mofetil to tacrolimus-mTOR immunosuppression after kidney-pancreas transplantation reduces the incidence of both BK and CMV viremia

Clin Transplant 2018

a retrospective single-center review of primary KP recipients with type 1 diabetes transplanted between December 2009 and June 2015

At one month post-transplant, recipients were converted from full-dose tacrolimus and MMF to an mTOR inhibitor, either sirolimus or everolimus and reduced-dose tacrolimus

CONCLUSION

the incidence of both BK and CMV viremia was significantly lower than that of a contemporaneously treated cohort using standard TAC-MMF immunosuppression

Graft and rejection-free survivals for kidney and pancreas grafts were both good and equivalent.

CMV and BKPyV Infections in Renal Transplant Recipients Receiving an mTOR Inhibitor–Based Regimen Versus a CNI-Based Regimen: A Systematic Review and Meta-Analysis of Randomized. Controlled Trials

CJASN

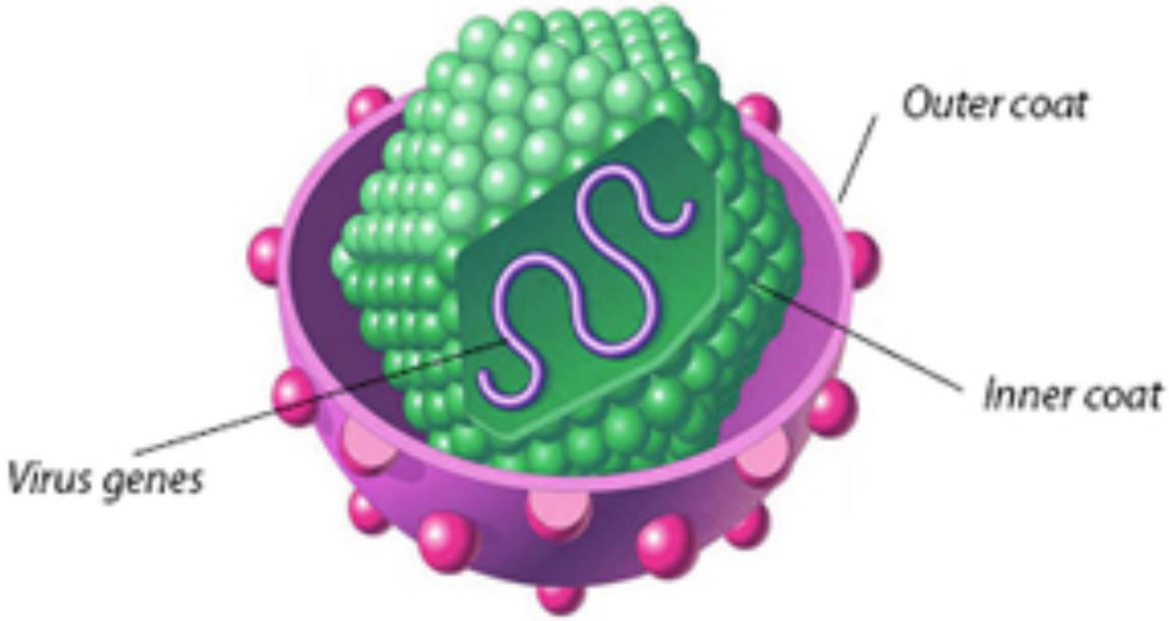
June 2, 2017

RTRs treated with everolimus had a more robust CMV-specific $CD8_+$ T cell response compared with those treated with cyclosporin or mycophenolic acid (MPA)

Sirolimus inhibited BKPyV replication in renal tubular epithelial cells, whereas tacrolimus activated it.

The analysis of this study did not find a significant difference in the incidence of BKPyV infection between an mTORi-based regiment and a CNIbased regimen ;
but decreased incidence of CMV infection.

HEPATITIS C VIRUS



Picture of one Hepatitis C Virus

Recurrent hepatitis C virus (HCV) is characterized by progre[illegible]
liver fibrosis and is associated with long-term graft
failure in liver transplant recipients. Due to the potential
antifibrotic properties through reductions in TGFβ and
procollagen, and antiviral activity via inhibition of phosphorylation
of NS5A phosphopeptides, sirolimus and everolimus
are thought to be beneficial in minimizing fibrosis and decreasing
HCV recurrence rates.

Although theoretically an advantageous therapy for hepatitis C virus–related liver allograft fibrosis and human immunodeficiency virus, mTORi use specifically for these indications is less attractive with modern treatments currently available.