Solid Organ Transplantasyonunda
İmmünsüpresif İlaçların Etki Mekanizmaları

Dr. Veysel Ersan

İnönü Üniversitesi

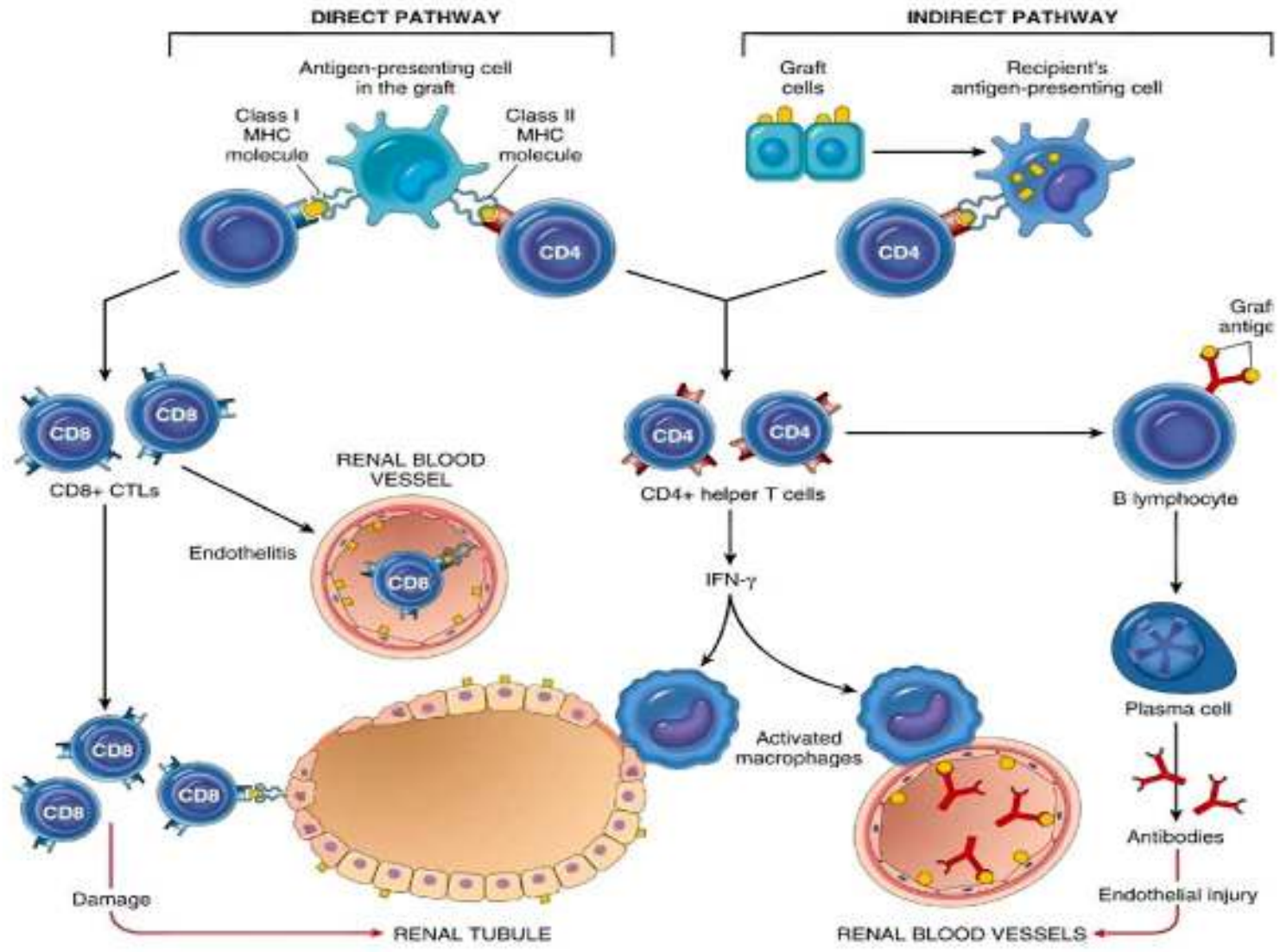
Karaciğer Nakli Enstitüsü

Malatya, Turkey

2021

9. TÜRKİYE EKMUD
ULUSLARARASI BİLİMSEL PLATFORMU
20-23 Mayıs 2021 - Online Kongre -

Amaç alloimmün yanıtı önlemek



Amaç alloimmün yanıtı önlemek

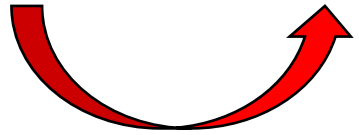
Direkt

Rec. T

MHC on Donor APC

İndirekt

Rec. APC Rec T



MHC on Donor cells

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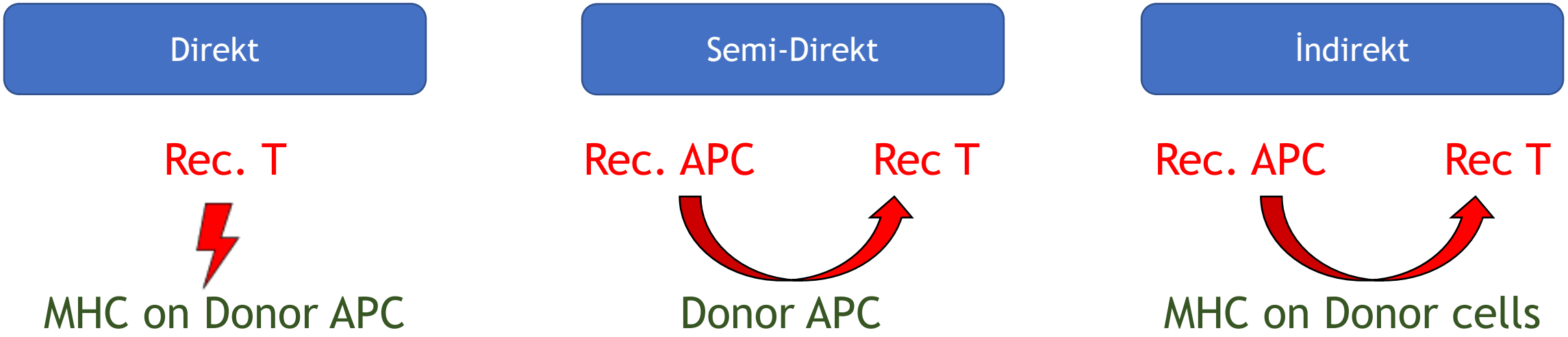
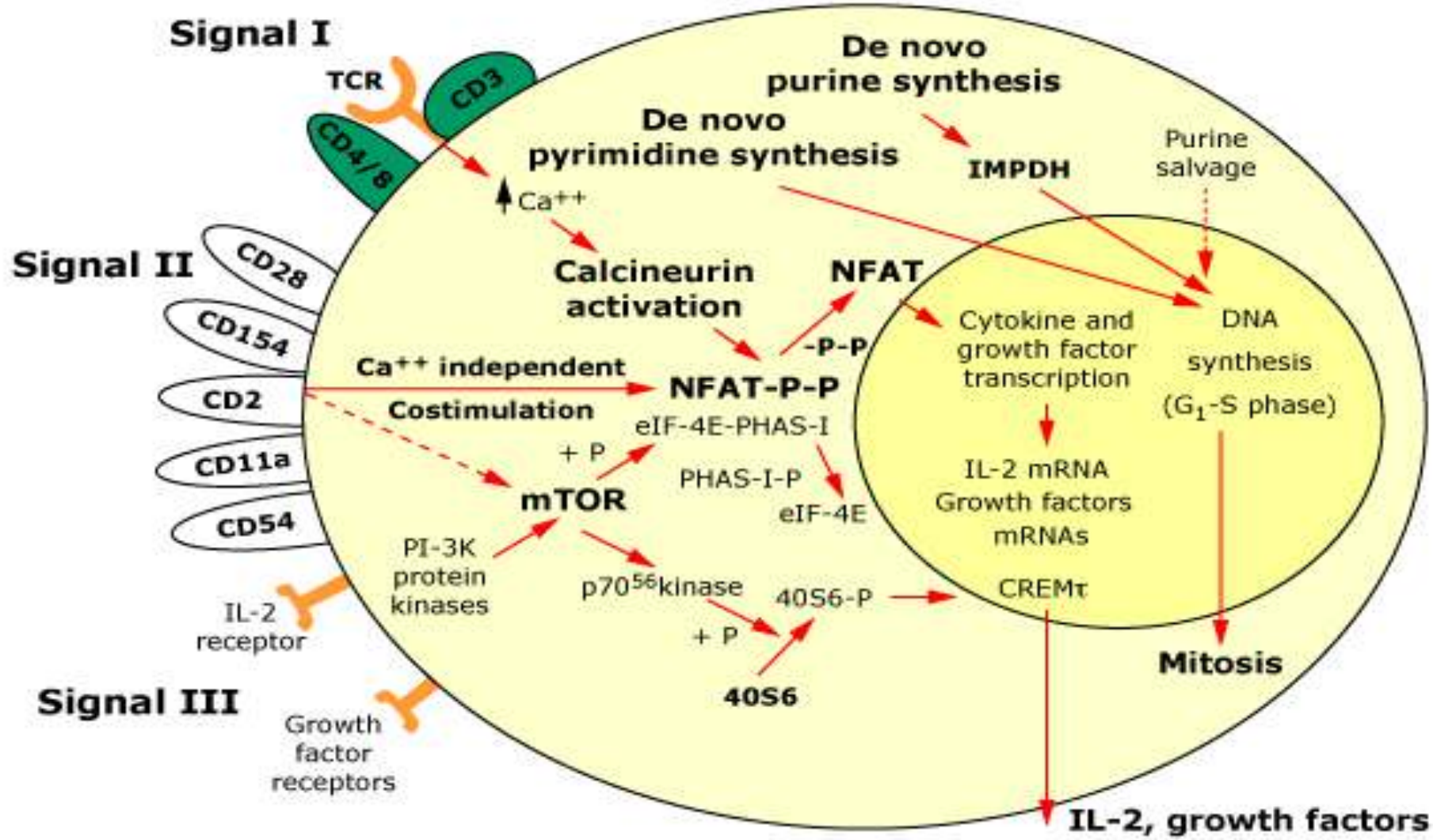


Herrera OB et. al A novel pathway of alloantigen presentation by dendritic cells. J Immunol. 2004 Oct 15;173(8):4828-37.

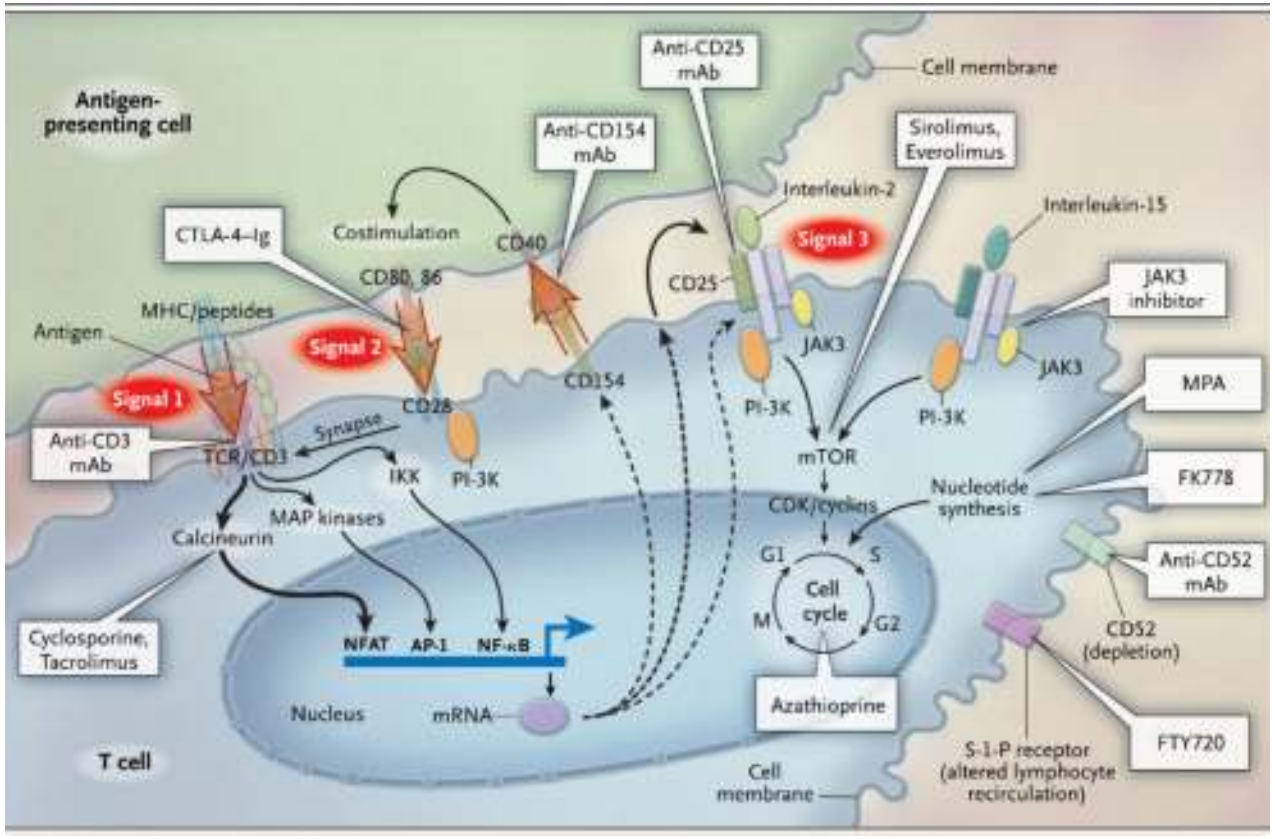


Sinyal I: APC tarafından T-hücre resptörüne antijenin sunulması

Sinyal II: Kostimülasyon - Ek APC ligandlarının, spesifik T-hücre reseptörlerine bağlanması

Sinyal III: Yeni sentezlenen IL-2 ve büyüme faktörlerinin yeni aktive olan T-hücrelerinde klonal gelişmeye neden olması

Etki mekanizmaları



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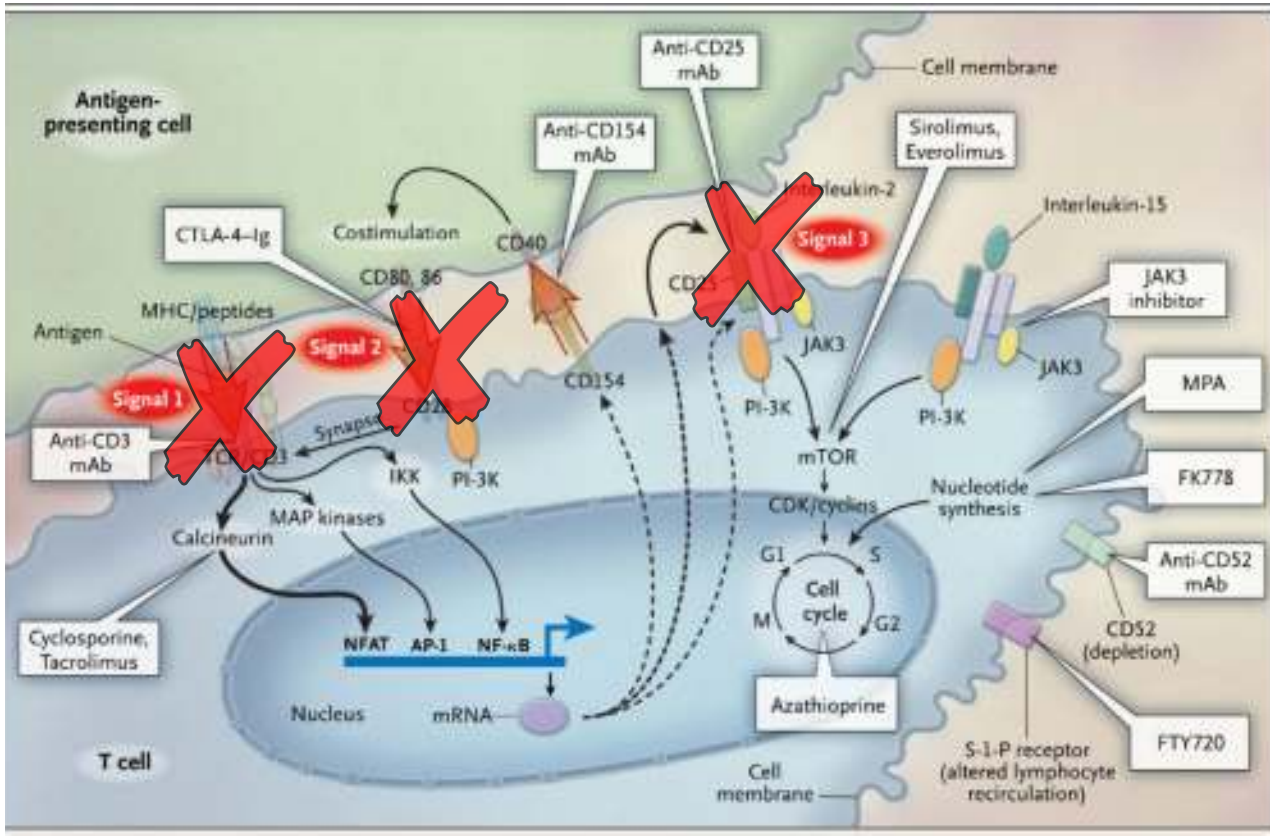

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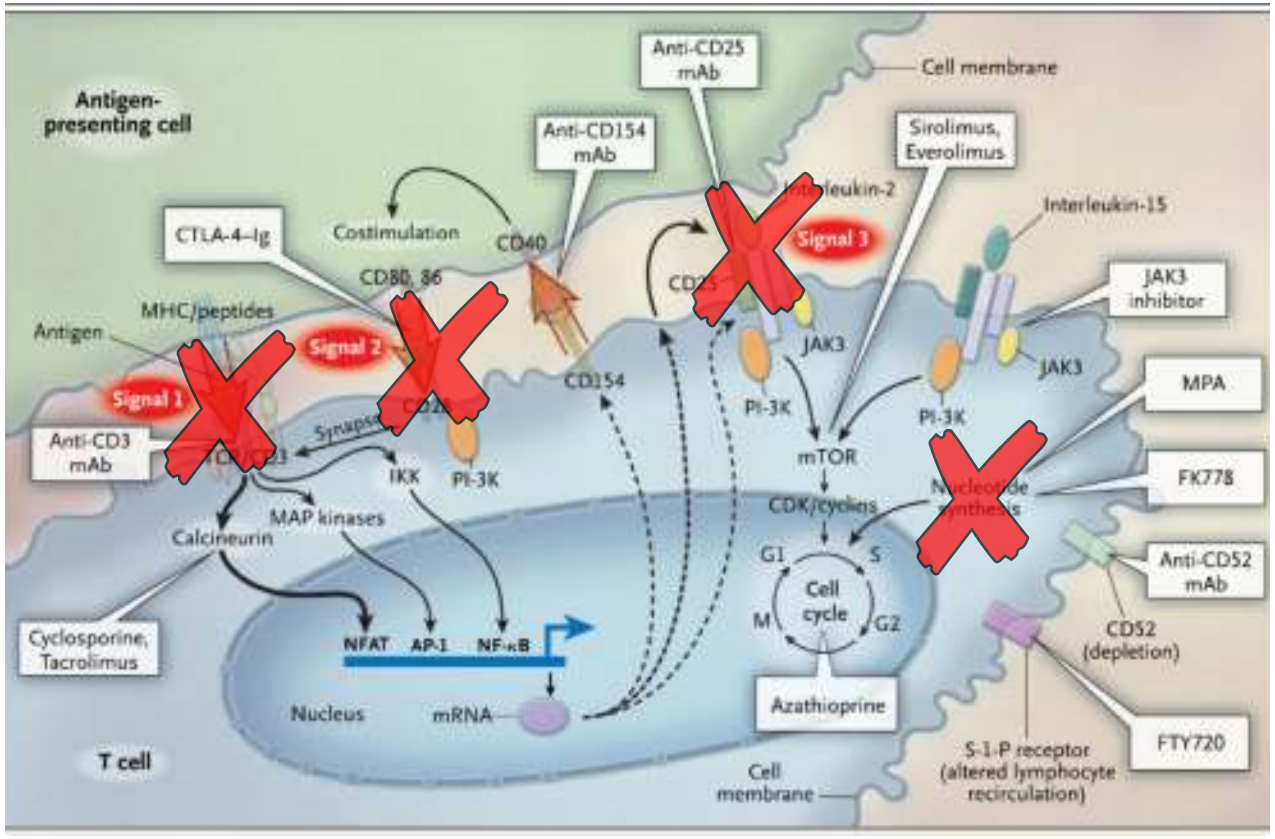
- **Nükleotidlerin sentezini sınırlayarak**



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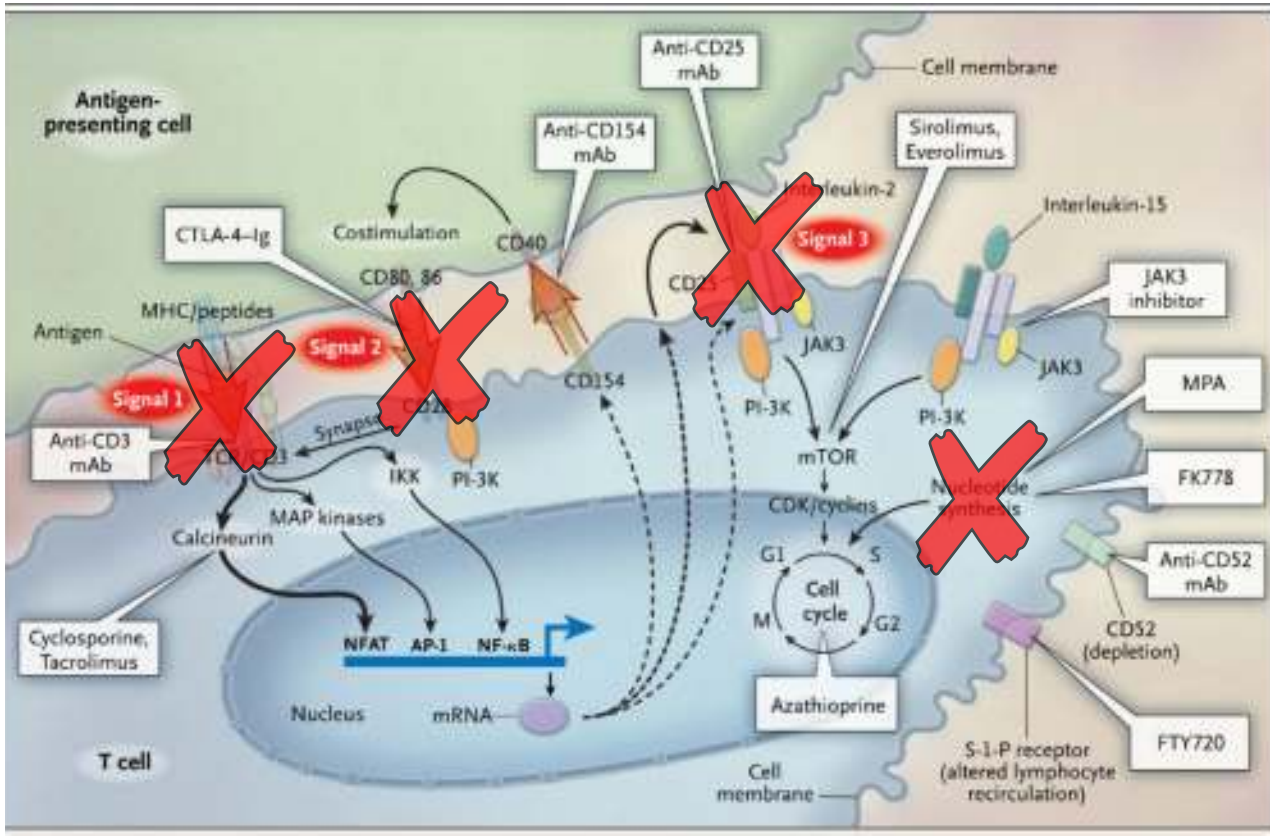
Etki mekanizmaları

- **Sinyal yolaklarını bloke ederek**
- **Nükleotidlerin sentezini sınırlayarak**
- **Bağışıklık hücrelerini tüketerek**



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Sınıflandırma

- **Küçük moleküllü ilaçlar**
- **Protein ilaçlar**

Küçük moleküllü ilaçlar

- Glukokortikoidler
- İmmünofiline bağlanan ilaçlar
  - Kalsinörin inhibitörleri: CsA, TAC
  - Mechanistic Target of rapamycin inhibitörleri: sirolimus, everolimus
- Nükleotid sentez inhibitörleri
  - Mycophenolic acid
  - Mycophenolate mofetil
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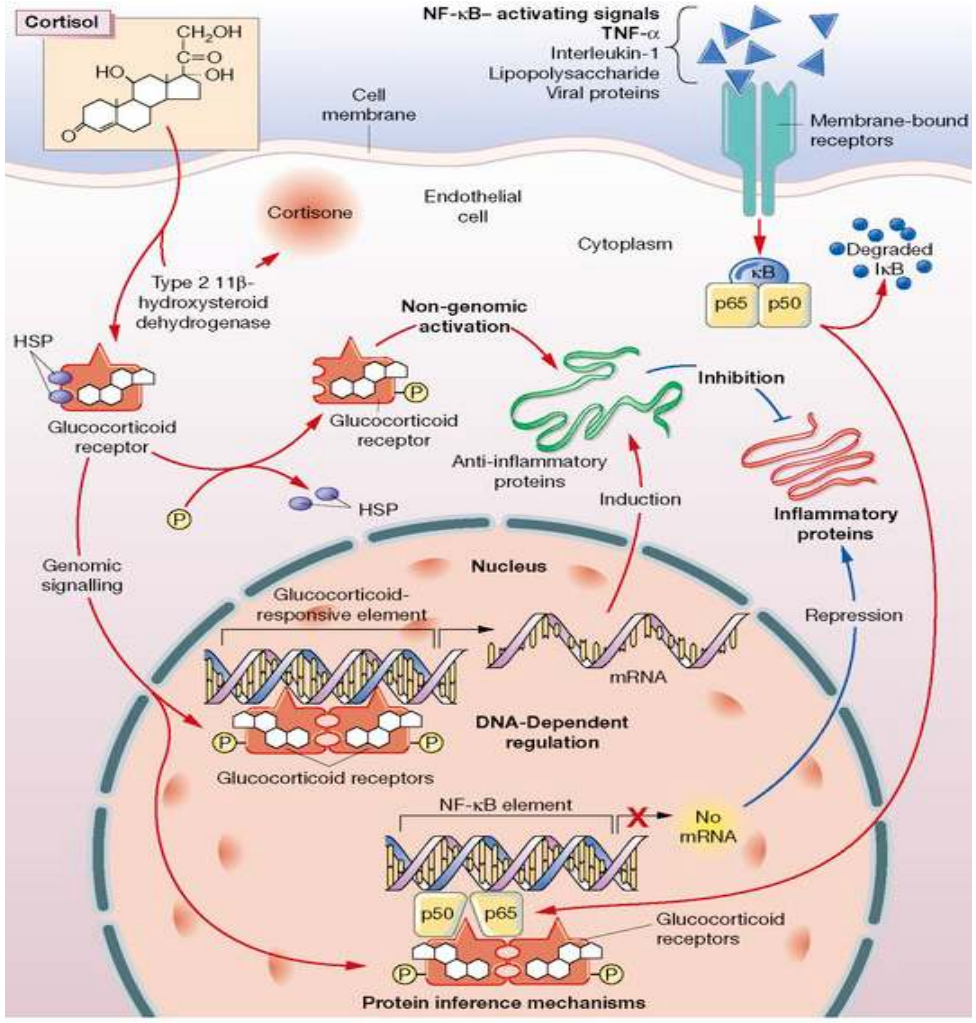
Glukokortikoidler

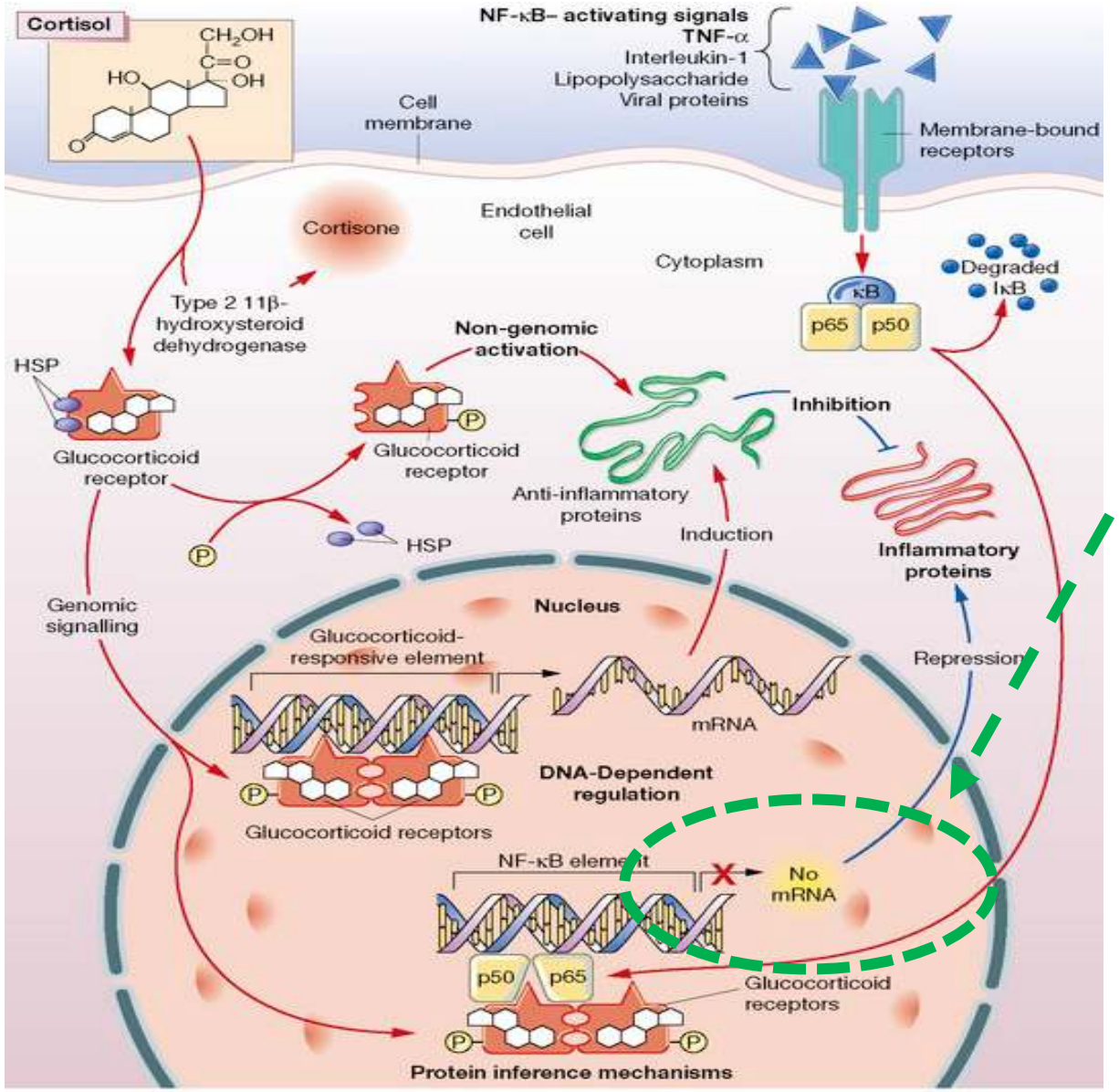
- İntrasellüler glukokortikoid reseptörüne bağlanır
- Nükleusa transloke olur
- Spesifik DNA dizileriyle doğrudan etkileşim kurar (glucocorticoid-responsive elements [GREs])



Glukokortikoidler

- **Gen transkripsiyonu üzerindeki etkiler**
  - **Proinflamatuar genlerin promoter bölgelerine bağlanma ve bloke etme (IL-1 alfa ve beta)**
  - **Antiinflamatuar gen ürünlerini kodlayan genlerin promoter dizilerine transkripsiyon faktörlerinin alınması**
  - **Neredeyse bilinen tüm inflamatuar sitokinlerin sentezinin inhibisyonu**
    - **Nuclear Factor-kappa-B (NF-kB)**
    - **Activator protein-1 (AP-1)**
- **Post-translasyonel etkileri**
  - **mRNA'nın kararlılığını azaltır**
    - **IL-1**
    - **IL-2**
    - **IL-6**
    - **IL-8**
    - **Tumor necrosis factor (TNF)**
    - **Granulocyte-macrophage colony-stimulating factor (GM-CSF)**

Glukokortikoidler



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İmmün sistem hücrelerine etkileri

- Leukocyte trafficking (lökosit trafiği?)
  - Vasküler endotele adezyonu engeller
    - Adezyon moleküllerine direkt etki
    - Sitokinlerin (IL-1, TNF) transkripsiyonunu inhibe ederek indirekt etki
- Nötrofil
  - Migrasyonu engeller
- Monosit / Makrofaj
  - Migrasyonu engeller
  - MHC-II antijen sunumu ⬇

İmmün sistem hücrelerine etkileri

- B lenfositler ve Ig
  - Uzun süreli tedavilerde B lenfosit sayısında azalma
  - IgG ve IgA seviyelerinde azalma, IgM çok etkilenmez
- T lenfositler
  - Yüksek dozlarda kullanıldığında hızlı tükenmeye neden olur
    - IL-2 inhibisyonu
    - Apoptozis indüksiyonu
    - Lenfoid dokulardan salınımı bozar

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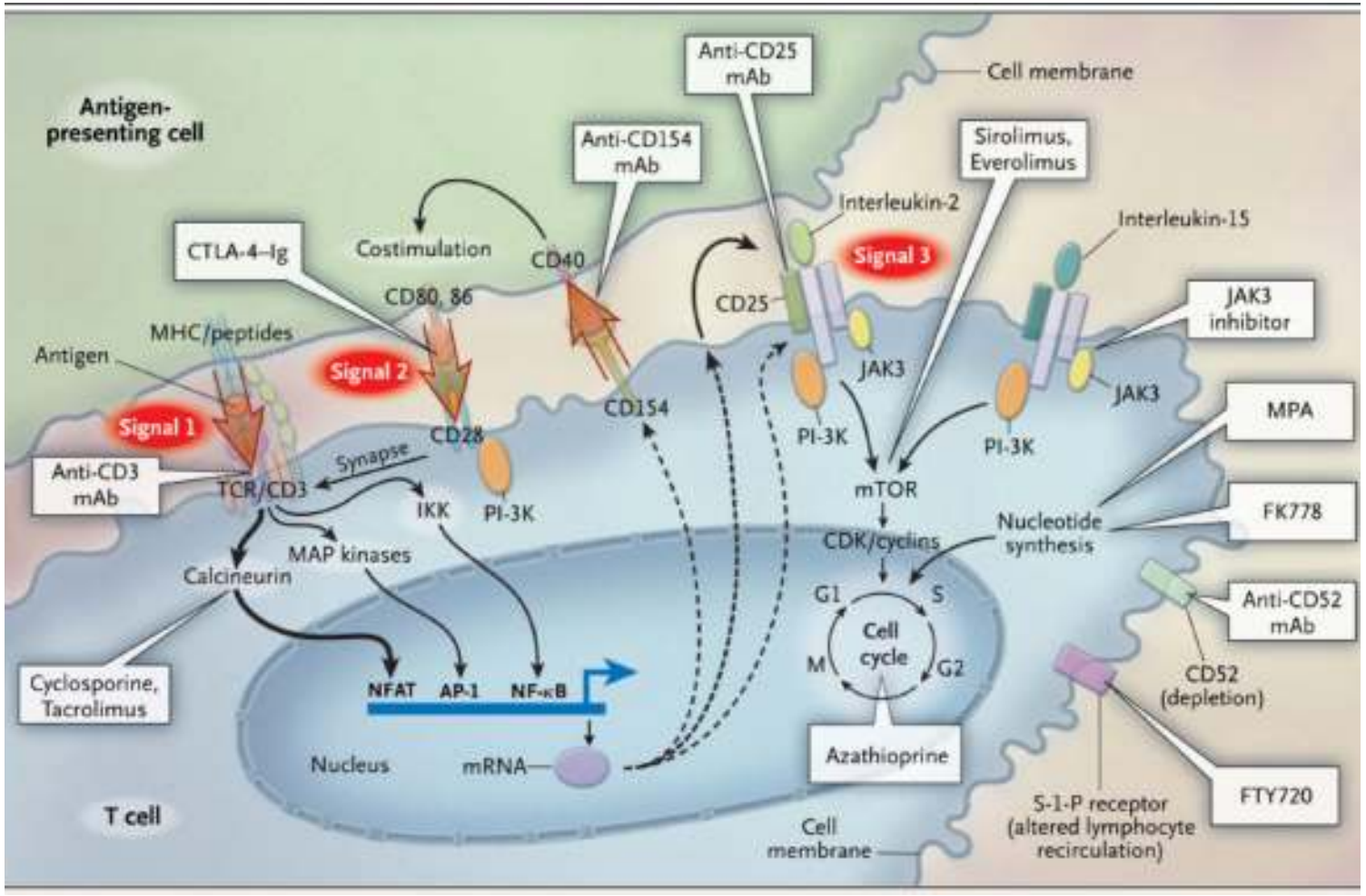

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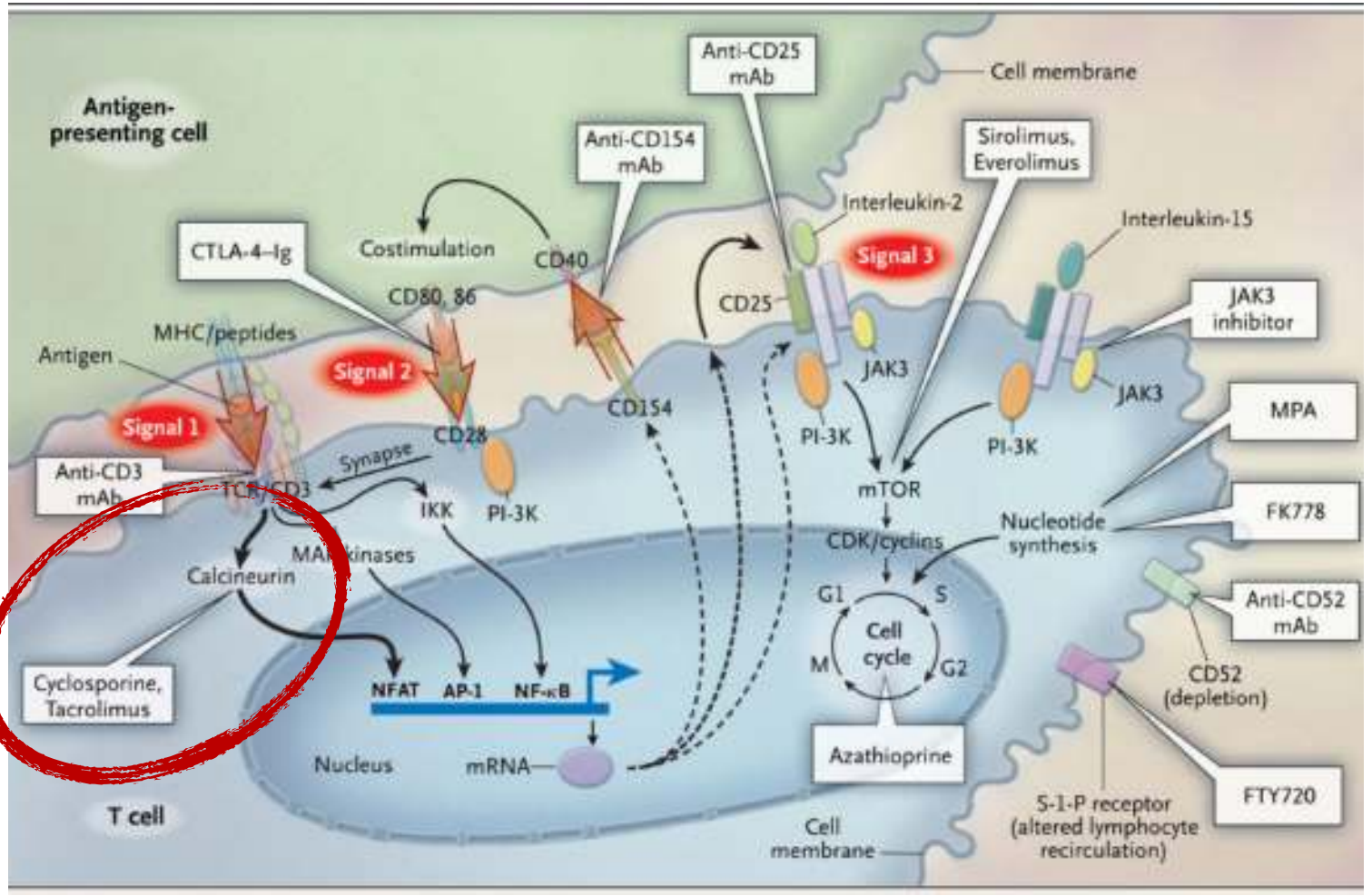

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Siklosiporin

- Tolypocladium inflatum

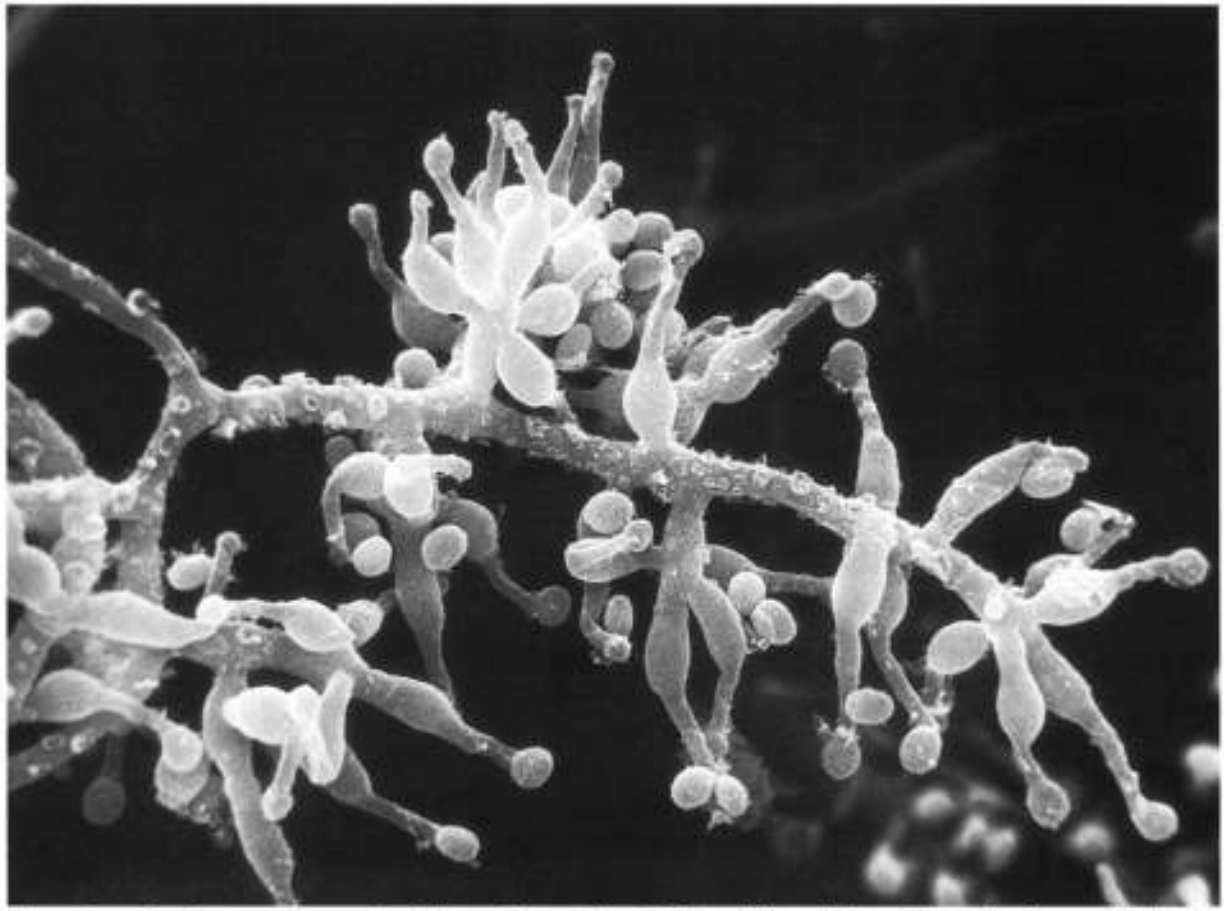
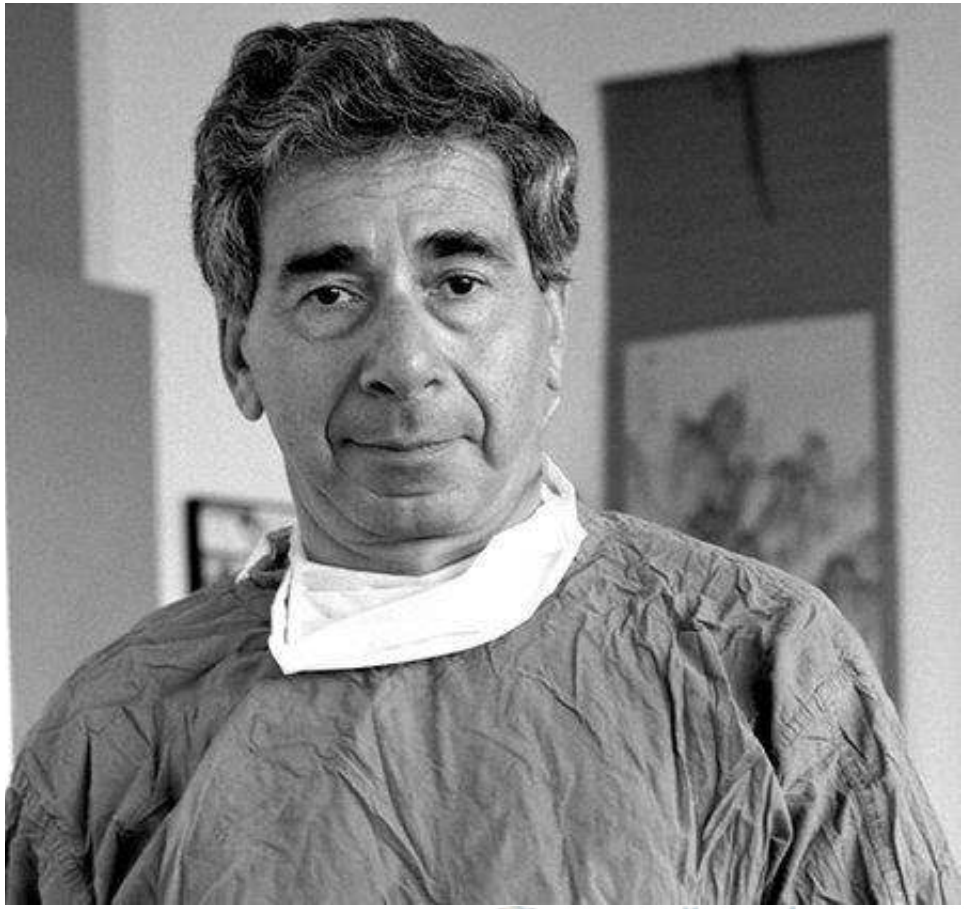


Fig 1 Scanning electron micrograph of the producer strain of *Tolypocladium inflatum* Gams showing conidiophores, phialides and conidia. x 5000 Photograph by courtesy of M. Dreyfuss and U. Strahm, Sandoz Ltd and R. Guggenheim and G. Lüönd, University of Basel (from Borel, J. F., 1983).

- Sir Roy Yorke Calne



Siklosiporin

- **Sir Roy Yorke Calne**

Volume 12, Part 1, February 1998

The Discovery and Development of Cyclosporin

HENRY T. TRIBE

Wolfson College, Cambridge

MYCOLOGIST FEBRUARY 1998

Prior to 1976, knowledge of cyclosporin was confined to Sandoz. In that year a classical paper was published (Borel, Feurer, Gubler & Stähelin, *Agents Actions* **6**, 468) in which the properties of cyclosporin were summarised.

Cyclosporin

1. was selective for lymphocytes, mainly for T-helper cells but sometimes for T-effector cells
2. suppressed antibody- and cell-mediated immunity and chronic (but not acute) inflammation
3. inhibited the induction phase of lymphoid cell proliferation, affecting early mitogenic triggering but not mitosis
4. was not toxic to lymphocytes (its effect being reversible)
5. was effective on all mammals tested (mouse, rat, guinea pig, rabbit, monkey, dog)
6. had no cardiovascular, psychotropic or other pharmacological effect which would seriously limit its effectiveness in man.

These main properties of cyclosporin were outlined orally to a meeting in which Dr David White, of Sir Roy Calne's Cambridge transplantation group, was present. Immediate interest was shown. Cyclosporin was supplied to the

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Agents and Actions
vol. 6/4 (1976)
Birkhäuser Verlag, Basel

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Biological Effects of Cyclosporin A: A New Antilymphocytic Agent

by J. F. Borel, Camille Feurer, H. U. Gubler[1]) and H. Stähelin
Biological and Medical Research Division Sandoz Ltd, CH-4002 Basle, Switzerland

Abstract

The fungus metabolite cyclosporin A is a small peptide acting as a novel antilymphocytic agent. It strongly depressed appearance of both direct and indirect plaque-forming cells and produced a clear dose-dependent inhibition of haemagglutinin formation in mice upon oral administration. Skin graft rejection in mice and graft-versus-host disease in mice and rats were considerably delayed by cyclosporin A which also prevented the occurrence of paralysis in rats with experimental allergic encephalomyelitis. This compound was not only highly effective in preventing development of Freund's adjuvant arthritis, but in addition improved the symptoms in rats with established arthritis, although it is inactive in acute inflammation. This new agent contrasts with other immunosuppressives and cytostatic drugs in its weak myelotoxicity. Experimental evidence suggests that cyclosporin A, rather than being cytostatic or lympholytic, affects an early stage of mitogenic triggering of the immunocompetent lymphoid cell.

actions. Some of these results are presented here.

Materials and methods

As cyclosporin A is not water soluble, it was routinely administered as a suspension in a 0.5% solution of tragacanth. Azathioprine (Burroughs Wellcome, London) was also suspended in tragacanth, while cyclophosphamide (Asta-Werke, Brackwede) was dissolved in water. Control animals always received the solvent. The treatment schedules are indicated in the legends of each figure or table.

Mice of both sexes were usually 8–12 weeks old an female rats about 8–10 weeks; the animal strains used in t different experiments are indicated either in the meth description or in the respective legend.

The assay of localized haemolysis in gel (LHG), use to detect both direct and indirect plaque-forming cells (PFC), was described previously [2]. The same developing serum as indicated in the above reference was used for

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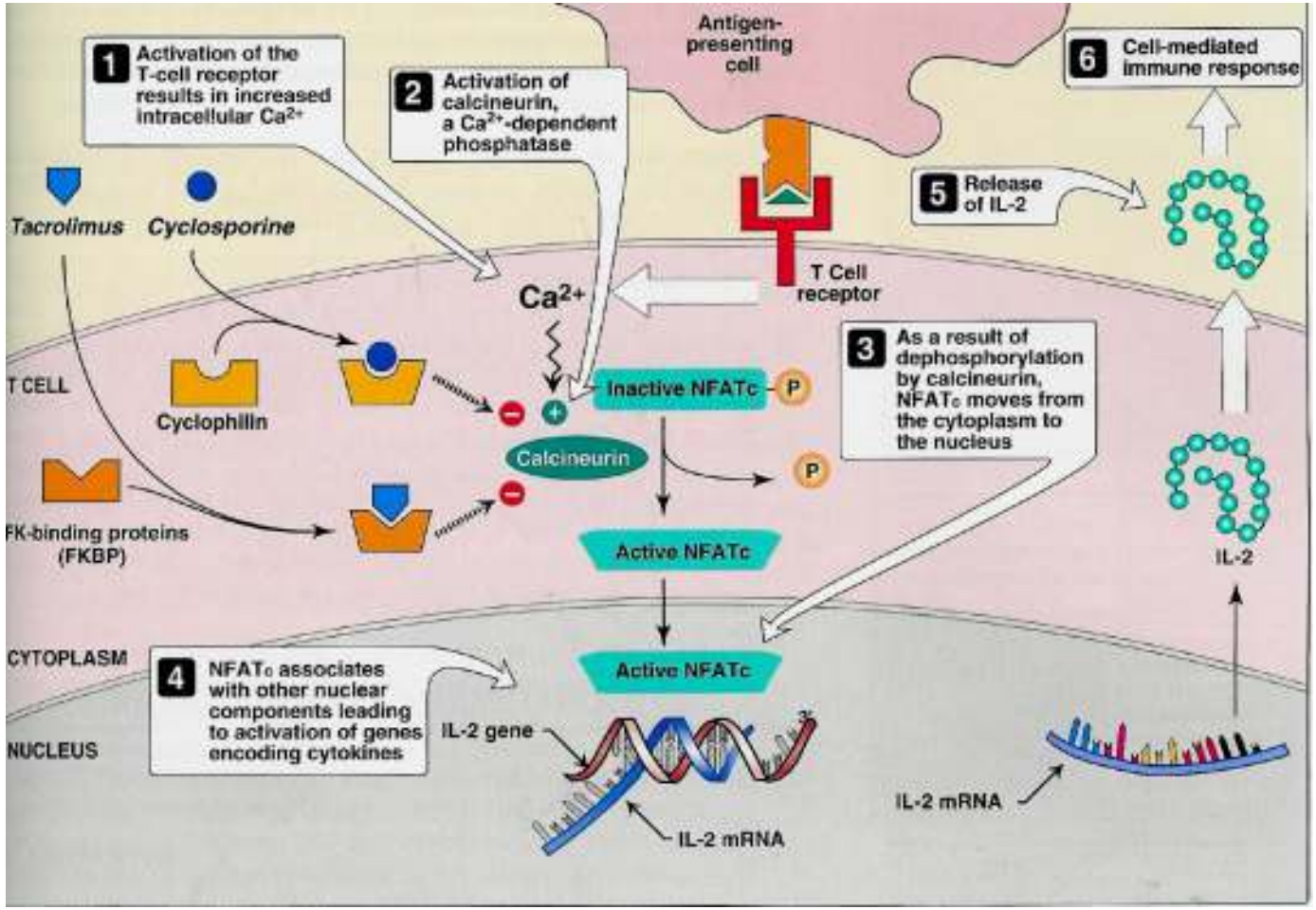

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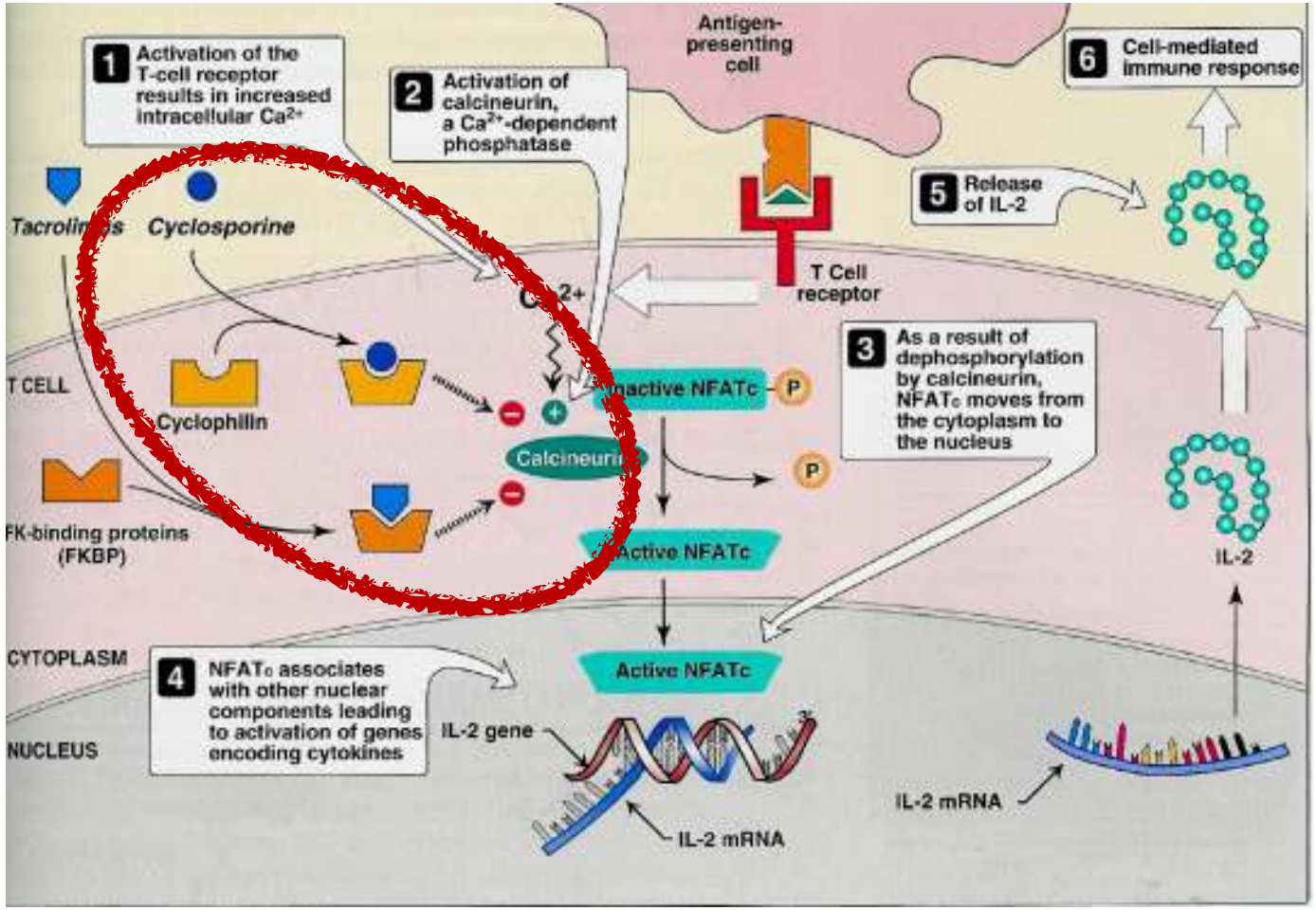

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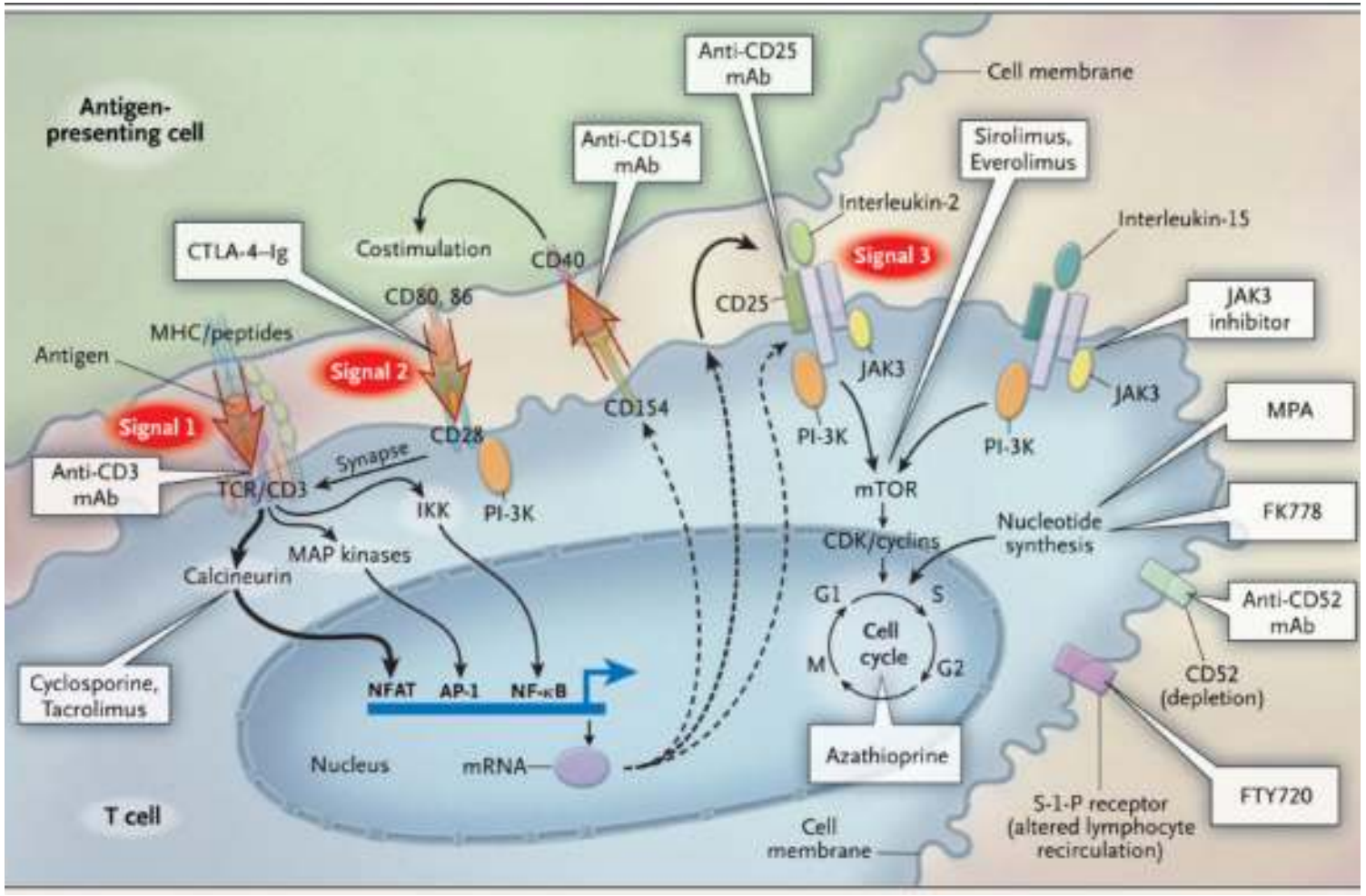

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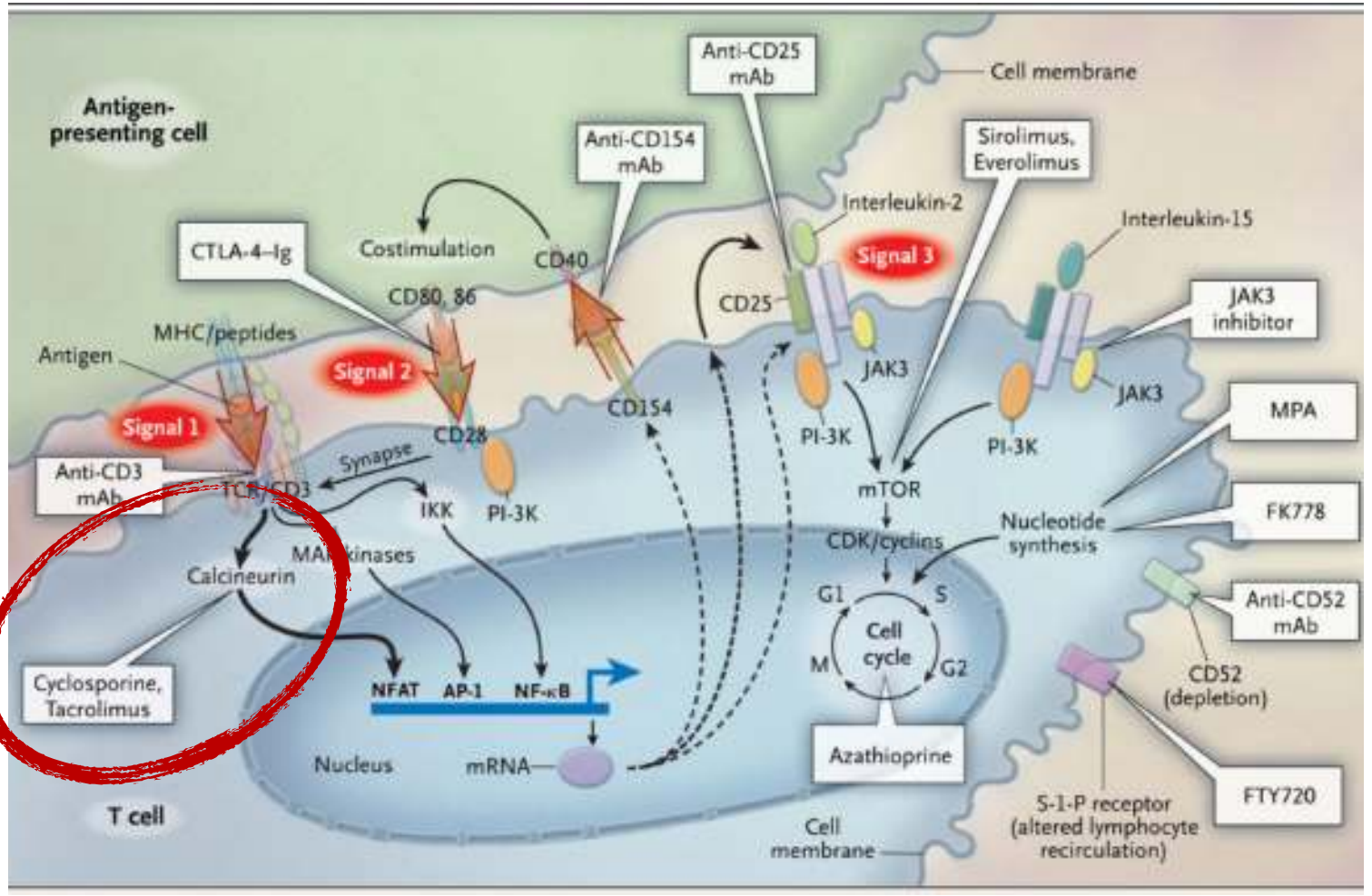

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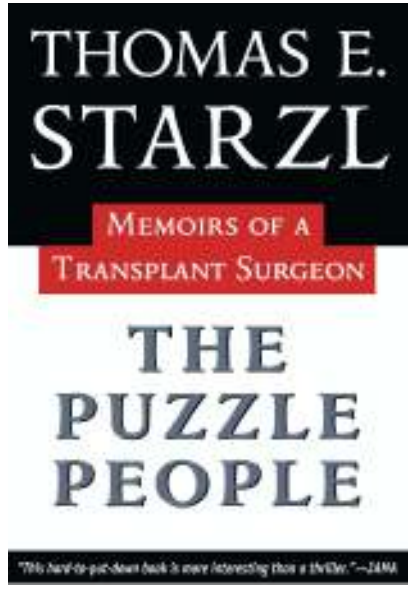
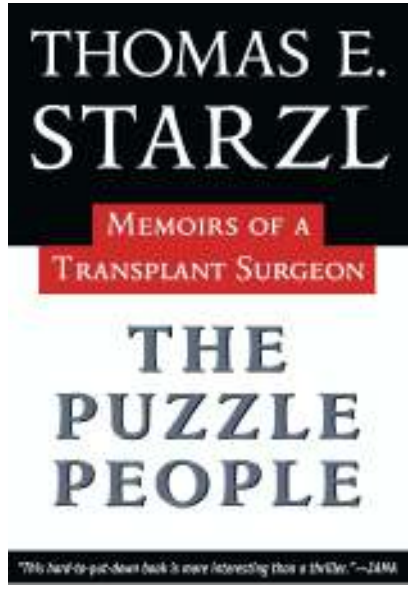
Takrolimus

Forty-five miles from Tokyo, the University of Tsukuba is located at the foot of the mountain from which the school and the village in which it is located take their name. Although the university is only two decades old, 10 to 15 percent of all the scientists in Japan are on its faculty. One reason is that more than 40 government institutes plus an additional 100 private institutes endowed and run by major corporations contribute to its campus. When I visited it in 1977, the village of Tsukuba was largely farmland. A decade later, it was an intellectual hotbed—and one of the fastest growing cities in the country.



1926 - 2017

Takrolimus



1926 - 2017

Sometime in the spring of 1986, I heard about a drug with the code name FR900506 that was discovered by scientists at the institute established on the Tsukuba University campus by the Fujisawa Pharmaceutical Corporation. Their project was to systematically screen natural substances in the soil for their anticancer or antirejection properties. One product of the search was a fungus (a

the discussion that followed, Calne said that he recently had tested the drug, which had been supplied to him by the Fison Corporation, an English pharmaceutical company which had obtained the drug through a trade agreement with Fujisawa. Calne was concerned about the drug's toxicity, and especially the violent vomiting which it caused in dogs. In the months to come, Calne became increasingly convinced of the drug's deficiencies. However, to me the properties of the drug, including the fact that it was one hundred times more potent per weight unit than cyclosporine, looked too promising to abandon. It was the beginning of a disagreement that lasted for more than three years.

- **“The burial ground for controversial drugs beckoned. If this was to be its fate, <u>the headstone would be easier to read because the name of FR900506 had been simplified to FK 506.</u>”**

Published in final edited form as:
Lancet. 1989 October 28; 2(8670): 1000–1004.

FK 506 FOR LIVER, KIDNEY, AND PANCREAS TRANSPLANTATION

Thomas E. Starzl[1,4], **Satoru Todo**[1], **John Fung**[1], **Anthony J. Demetris**[2], **Raman Venkataramman**[3], and **Ashok Jain**[1]

[1] Department of Surgery, University Health Center of Pittsburgh, University of Pittsburgh, Pennsylvania, USA

[2] Department of Pathology, University Health Center of Pittsburgh, University of Pittsburgh, Pennsylvania, USA

[3] Department of School of Pharmacy, University Health Center of Pittsburgh, University of Pittsburgh, Pennsylvania, USA

[4] Veterans Administration Medical Centre, Pittsburgh, Pennsylvania, USA

Abstract

Summary

FK 506 was given for immunosuppression in 14 liver recipients. The drug was used in the first 10 cases because the recipients under conventional immunosuppression had rejection, nephrotoxicity, or both. This salvage therapy was successful in 7 of the 10 attempts. 2 of the 10 patients in the original salvage group as well as 4 new patients underwent fresh orthotopic liver transplantation under FK 506 plus low-dose steroids from the outset. None of these 6 patients had rejection although 1 with

Takrolimus

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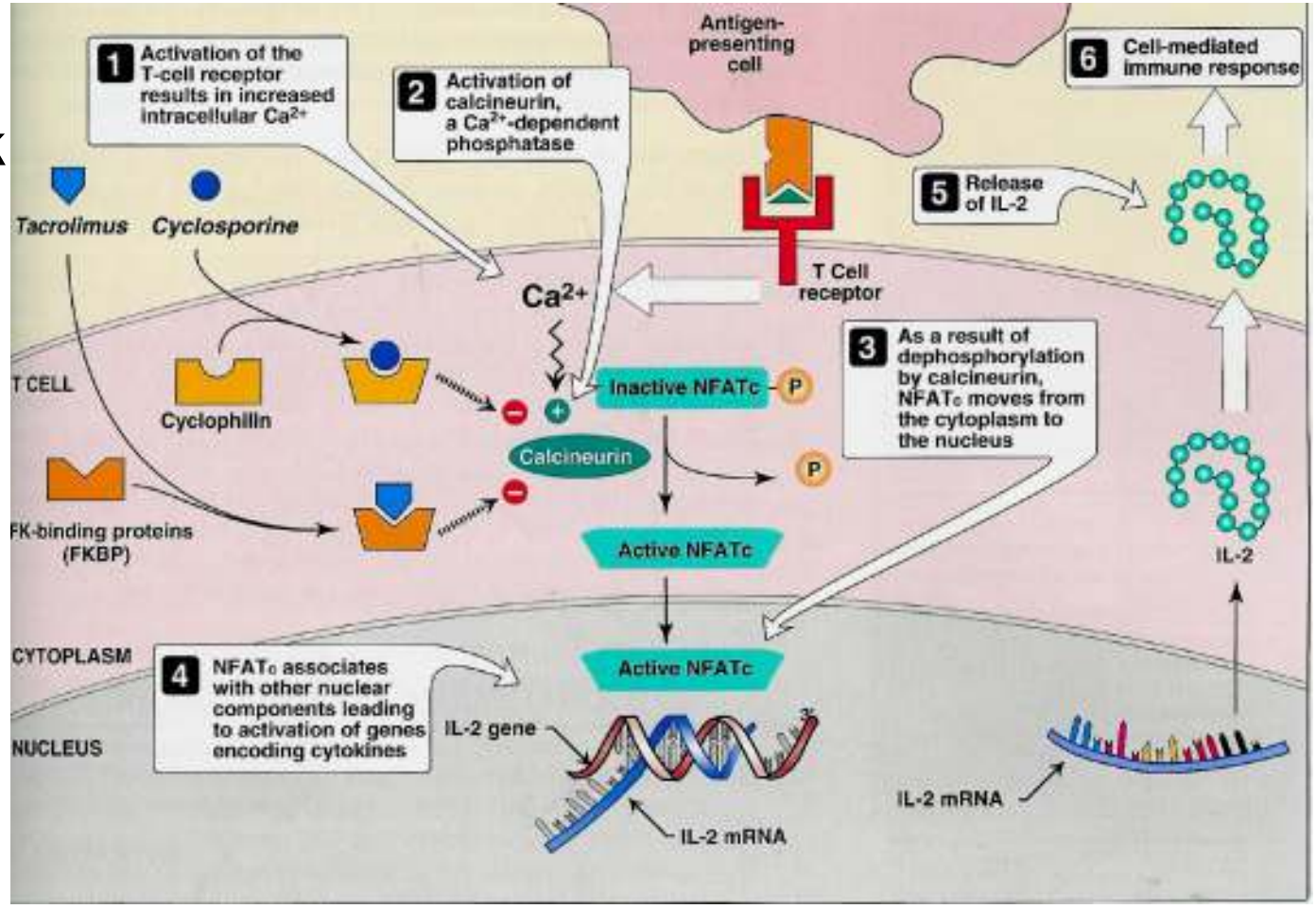

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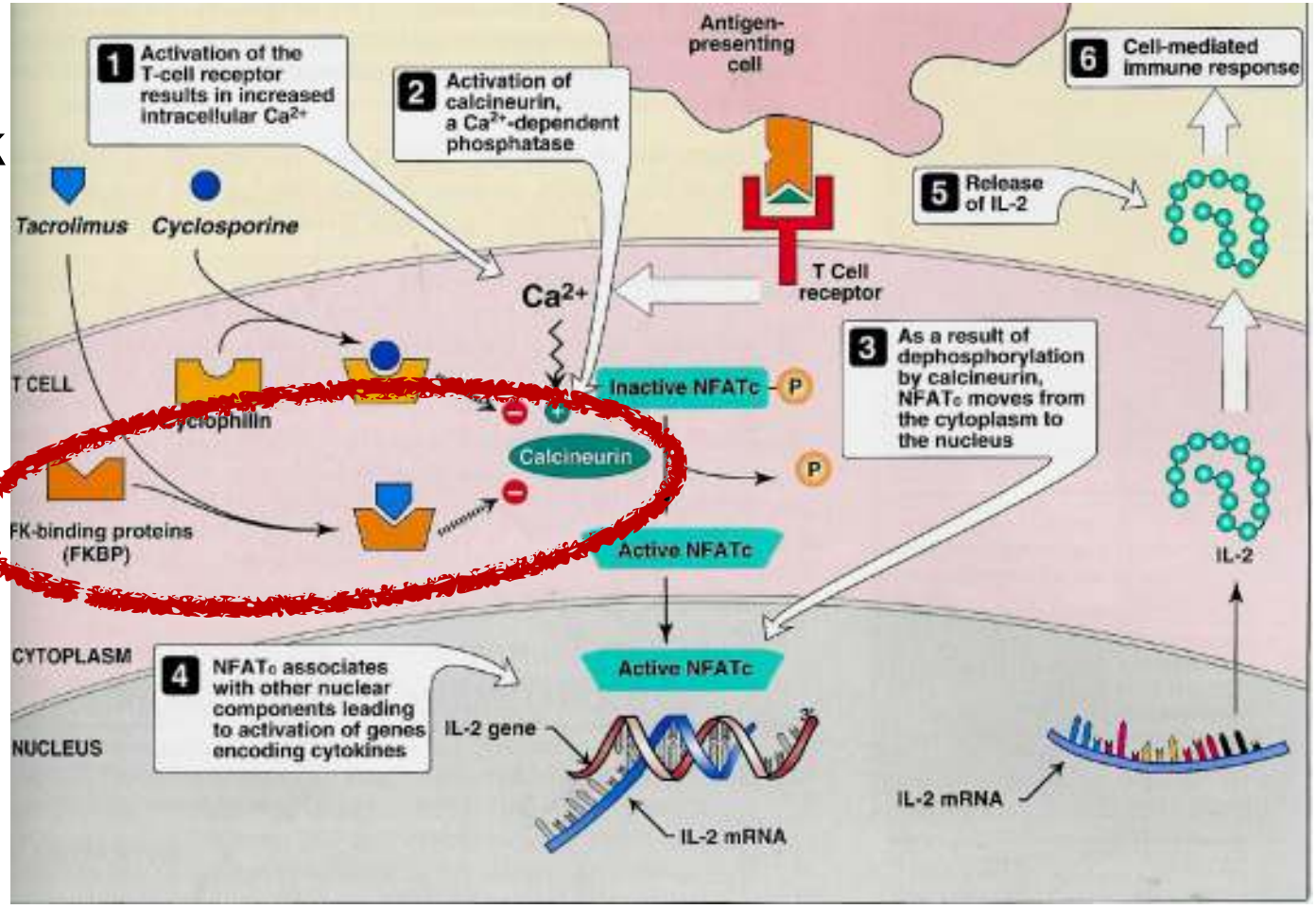

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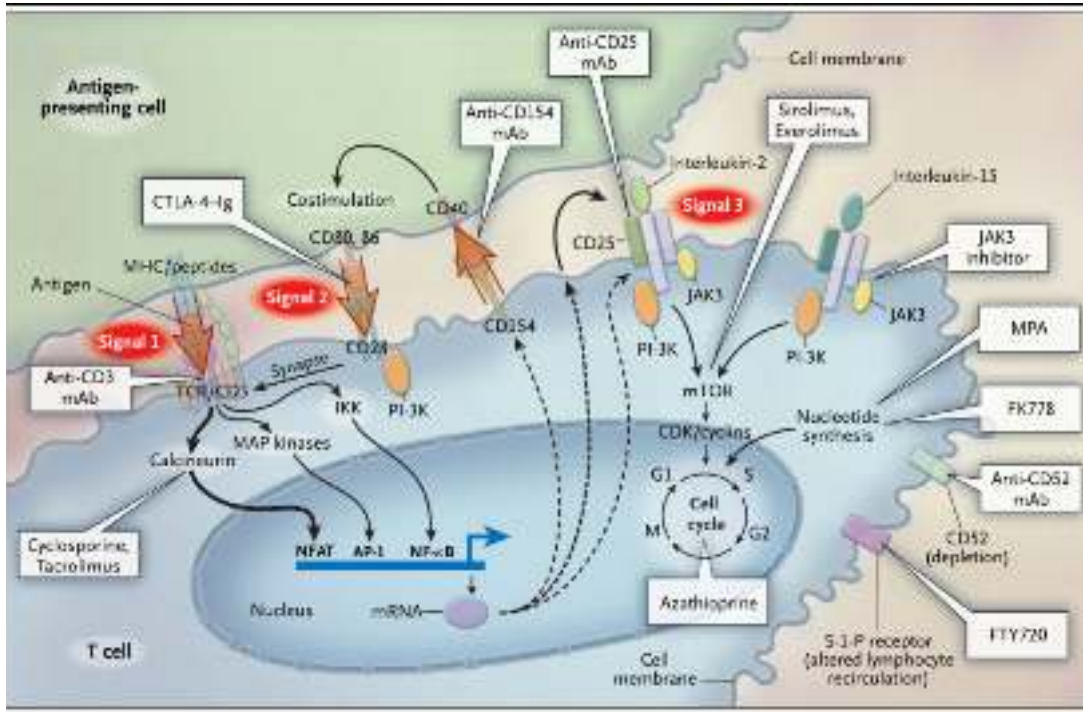
mTOR

- Hücresel homeostaz sensörü
- Hücresel stresi algılar
  - Büyüme
  - Proliferasyon
  - Beslenmeyi koordine eder
- İmmünsüpresyon
  - Siklin-E ve siklin-A bağımlı kinazları kontrol eder.
  - G1 fazından S fazına geçiş
  - Lenfositlerin proliferasyonu ve aktivasyonu ⬇



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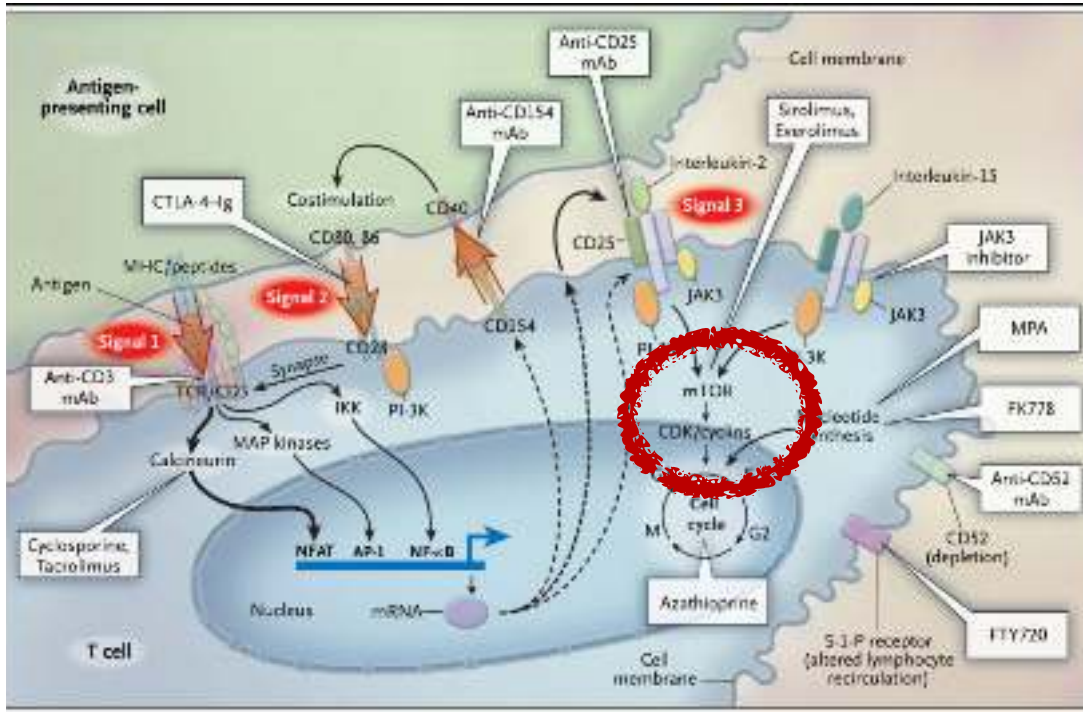
mTOR

- Hücresel homeostaz sensörü
- Hücresel stresi algılar
  - Büyüme
  - Proliferasyon
  - Beslenmeyi koordine eder
- İmmünsüpresyon
  - Siklin-E ve siklin-A bağımlı kinazları kontrol eder.
  - G1 fazından S fazına geçiş
  - Lenfositlerin proliferasyonu ve aktivasyonu ⬇



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Easter Island - Rapa Nui

mTOR inhibitörleri

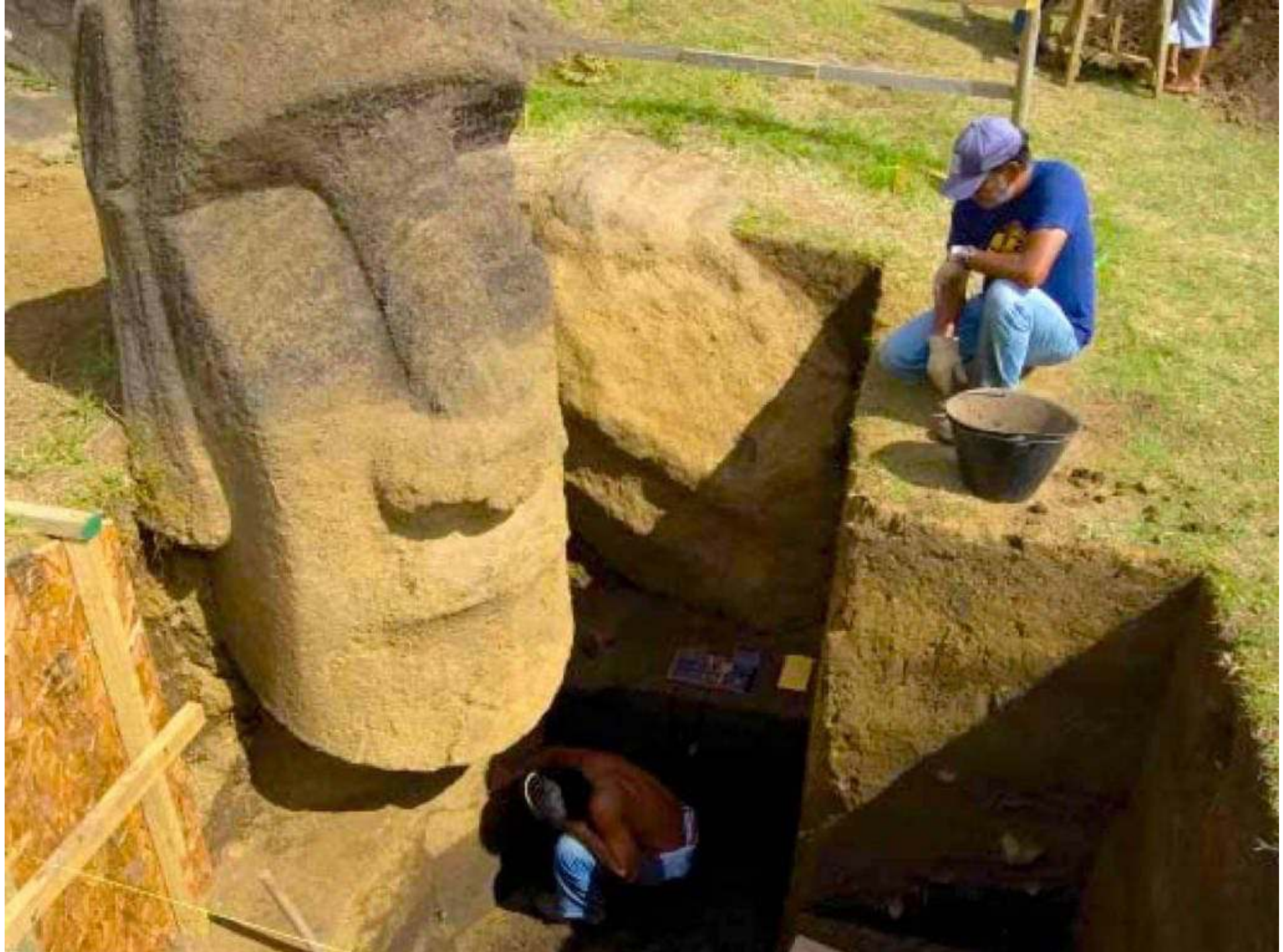
- Rapamisin, 1970'lerin başında Paskalya Adası'nda (Rapa Nui) elde edilen bir toprak örneğinden izole edildi ve güçlü bir anti-fungal metabolit olarak tanımlandı.

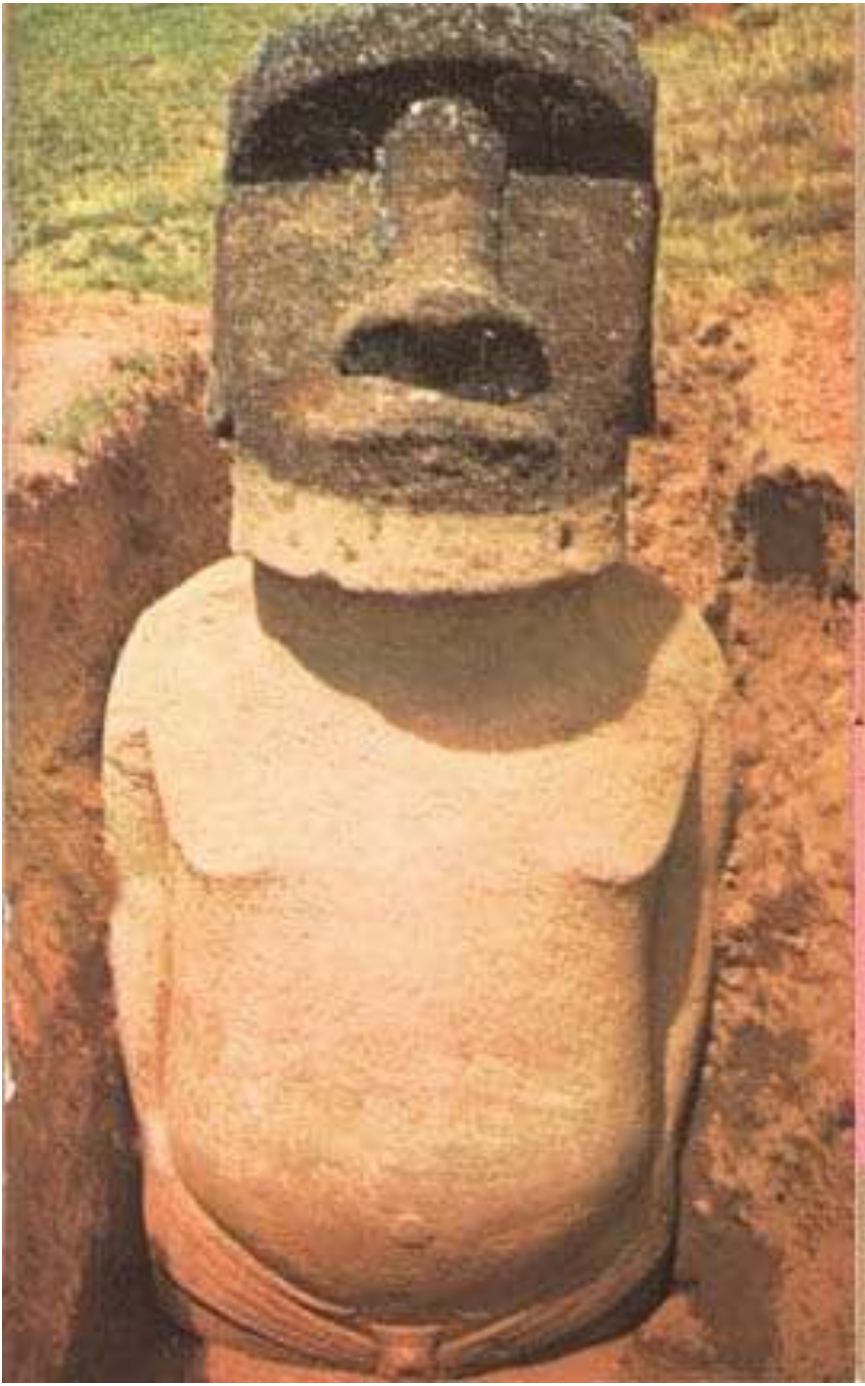
- Streptomyces hygroscopicus tarafından üretilen bu makrolidin hücre proliferasyonunu inhibe ettiği ve güçlü immünosupresif aktiviteye sahip olduğu bulunmuştur.

In this location were obtained, in January 1965, soil samples that led to discovery of rapamycin, a substance that inaugurated a new era for organ transplant patients.

Mysterious Connections

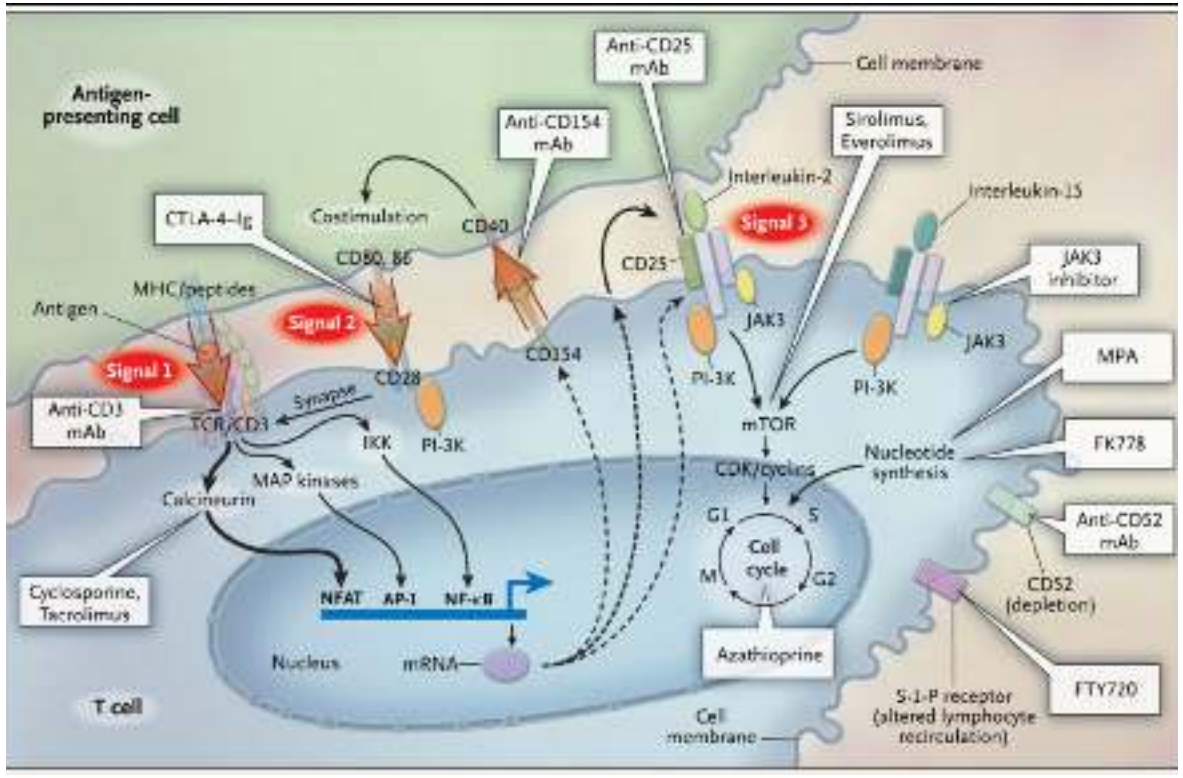
There has also been a mystery surrounding the writing system used on Easter Island during its inhabitance. Robert M. Schoch believed that the tablets with calligraphy could date back 10,000 years older than previously expected. And this would also make the island older. Schoch's epiphany came after exploring the ancient ***Turkish ruins of Gobekli Tepe***, due to seemingly feeling out of place in terms of where it is located. ***Schoch sees many similarities between the Moai and the pillars of Gobekli Tepe.***





mTOR inhibitörleri

- Sirolimus, Everolimus
  - FKBP'e bağlanır (TAC gibi)
  - IL-2 aracılı sinyal inhibisyonu
  - T ve B hücrelerinin sitokinler tarafından aktivasyonunu önler
  - Hücre siklusunu G1 fazında durdurur



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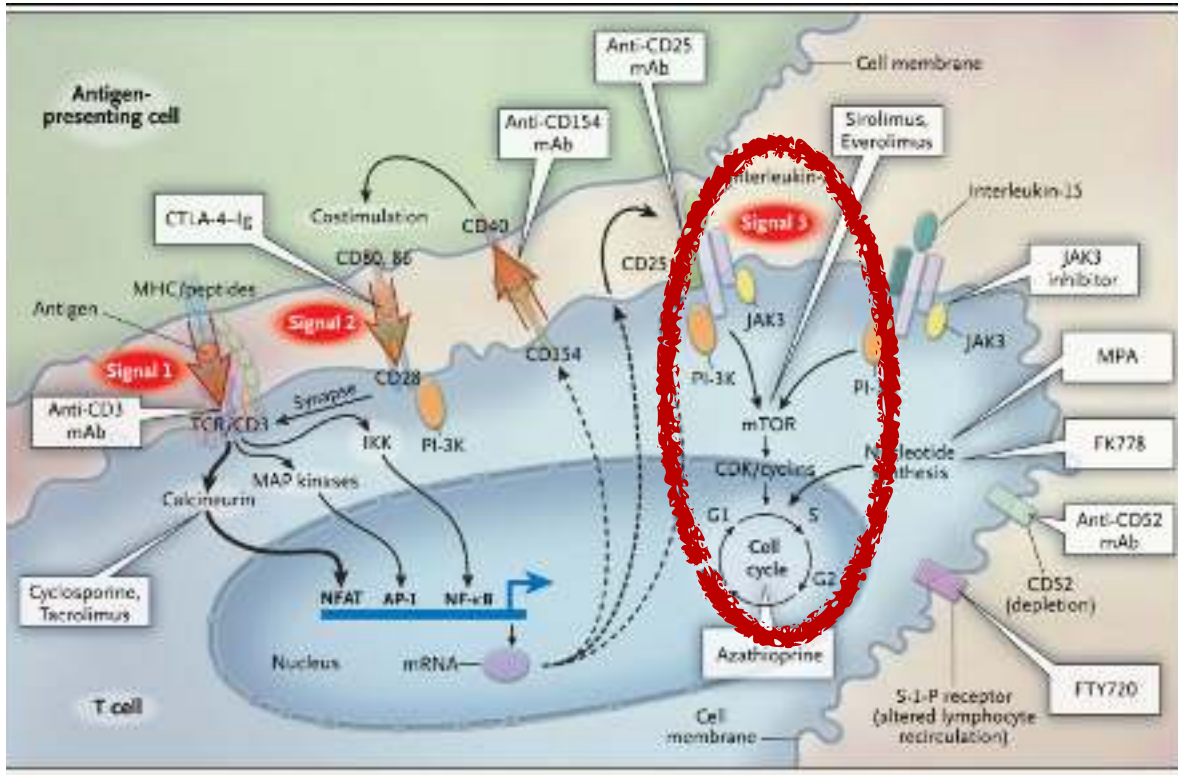

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Küçük moleküllü ilaçlar

- Glukokortikoidler
- İmmünofiline bağlanan ilaçlar
  - Kalsinörin inhibitörleri: CsA, TAC
  - Mechanistic Target of rapamycin inhibitörleri (mTORi): sirolimus, everolimus
- Nükleotid sentez inhibitörleri
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  - Mycophenolate mofetil
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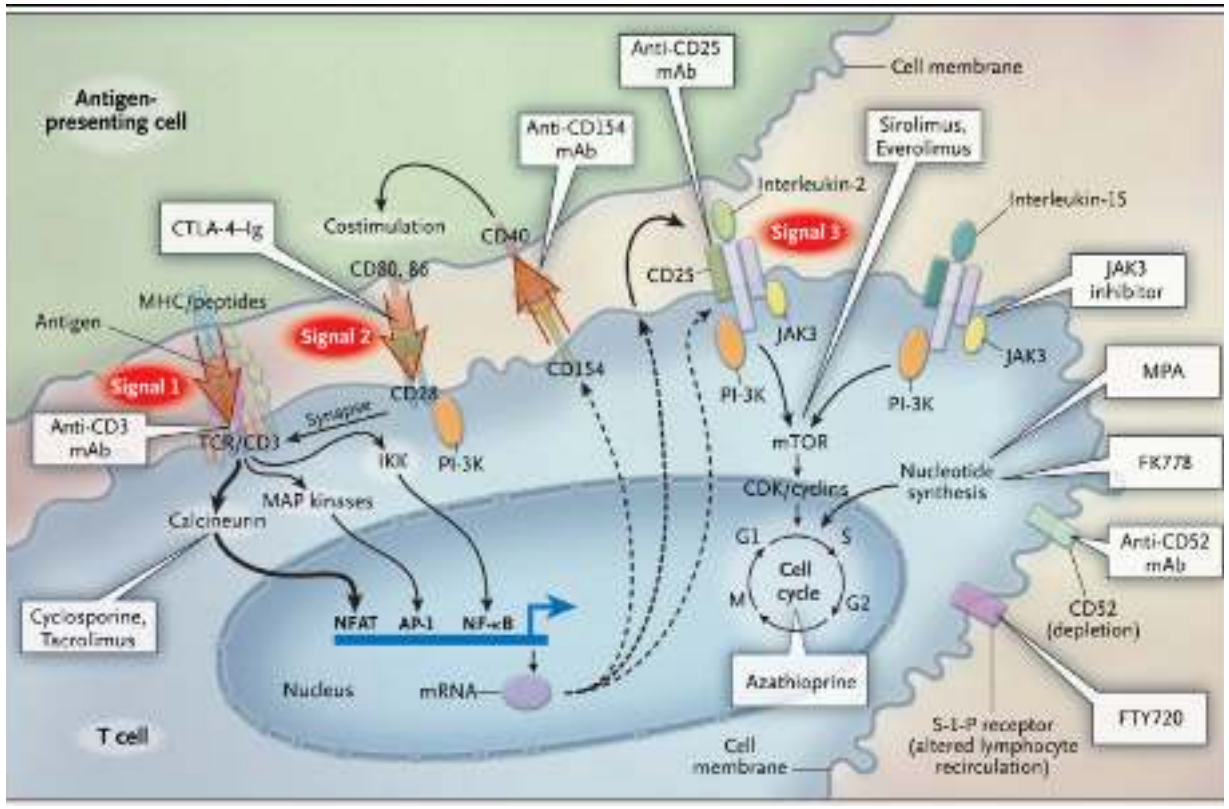
Mikofenolat mofetil (MMF) - Mikofenolat sodyum

- Aktif form olan mikofenolik asite (MPA) dönüşürler
- IMPDH inhibe ederek de novo pürin sentezini bloke eder
- B ve T lenfositlerde pürin kurtarma yolağı olmadığı için MPA özellikle bu hücrelerde replikasyonu inhibe eder
- Hem hücresel immünite hem de antikor üretimi sinyal-3 üzerindeki etki ile baskılanmış olur.



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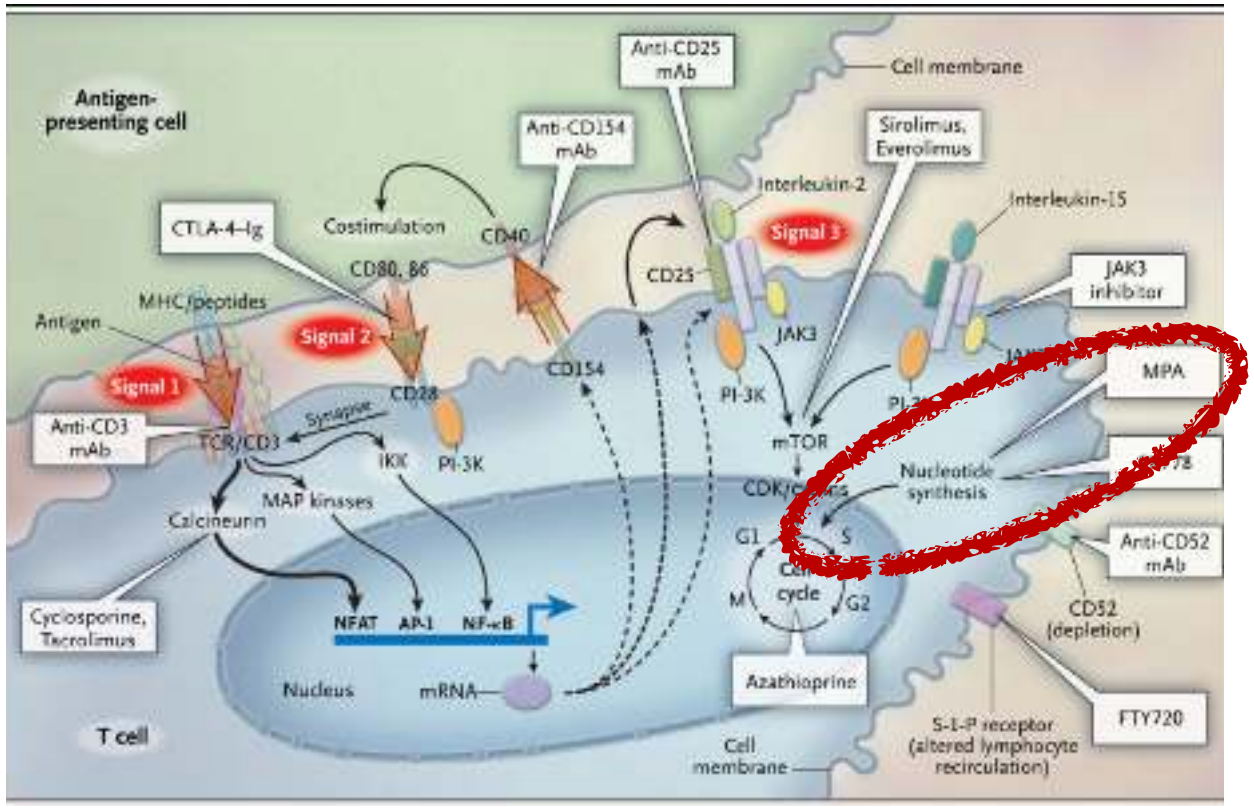

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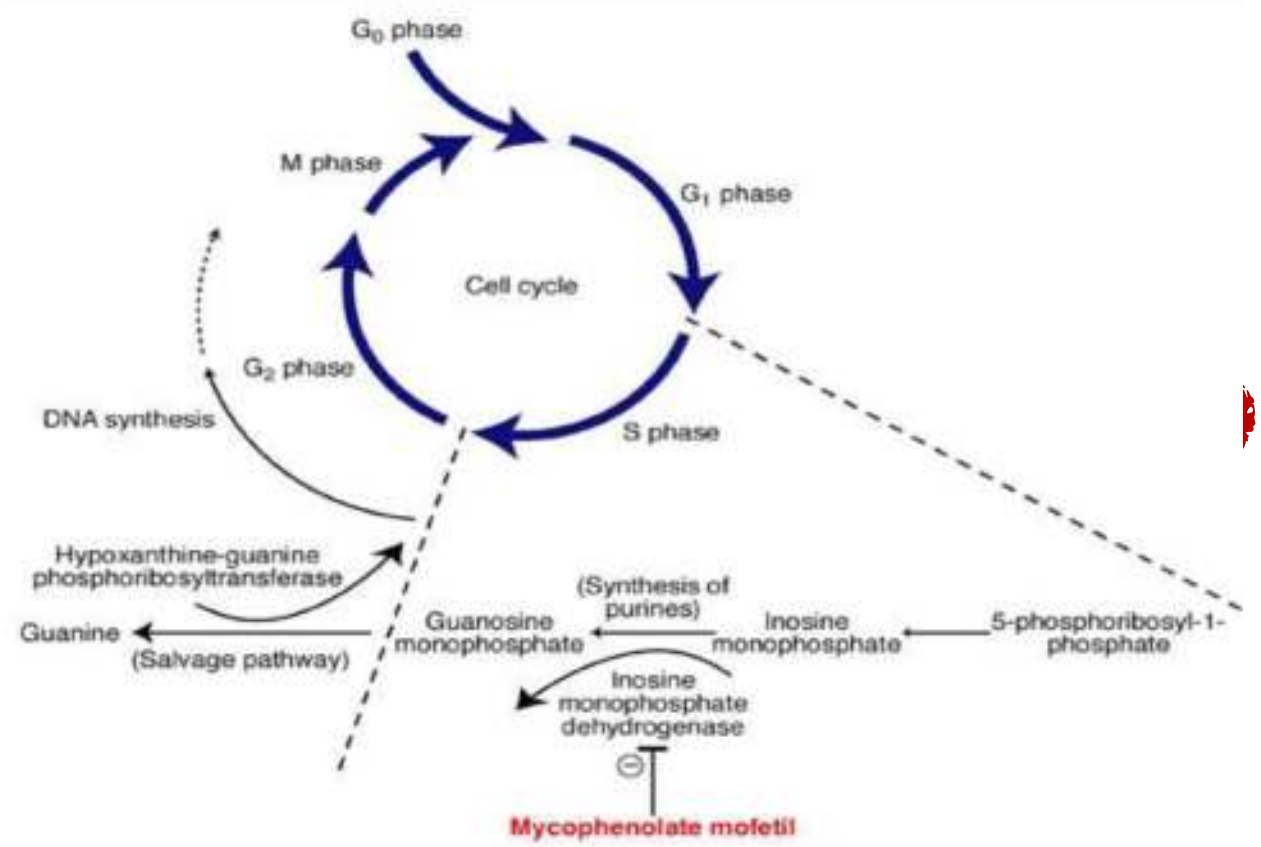
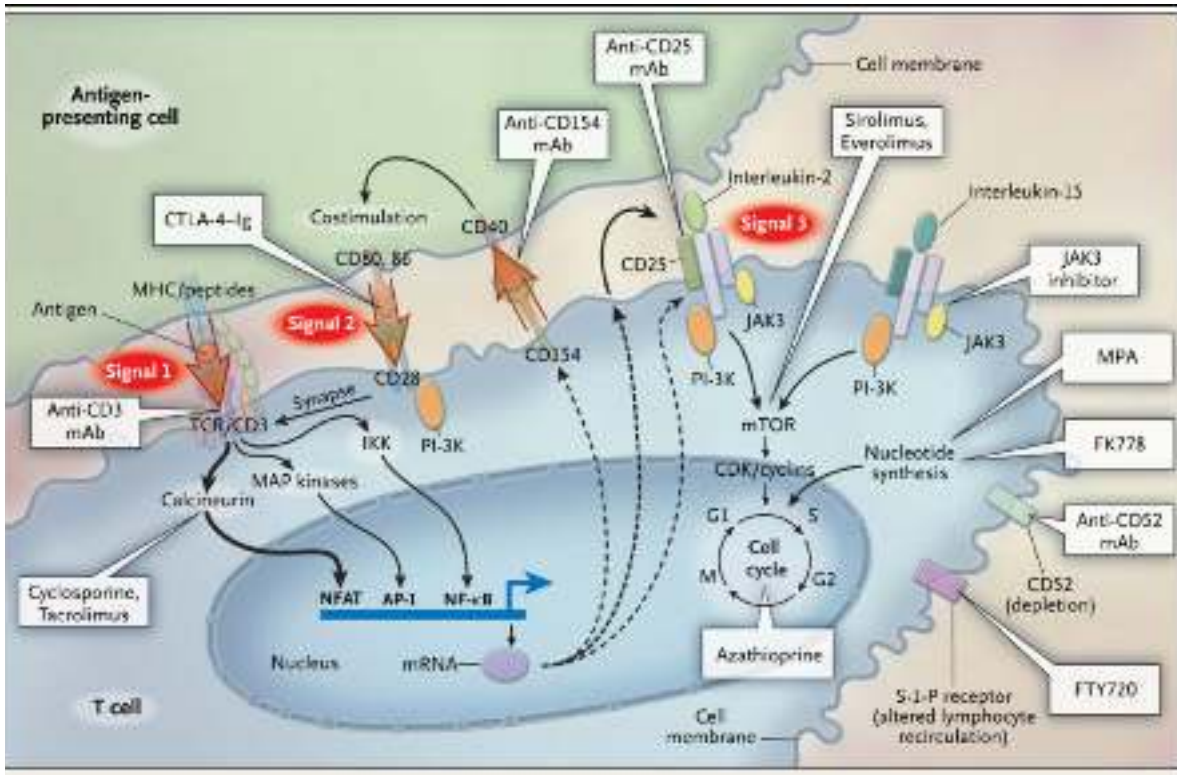


Azatiyoprin (İmuran)

- Sir Roy Yorke Calne

- En eski immünsüpresif ilaçlardan birisidir.
- IMPDH inhibisyonu yaparak pürin sentezini engeller.
- Sinyal-3 yolağı üzerinden etki eder
- Hücresel ve humoral immüniteyi baskılar.



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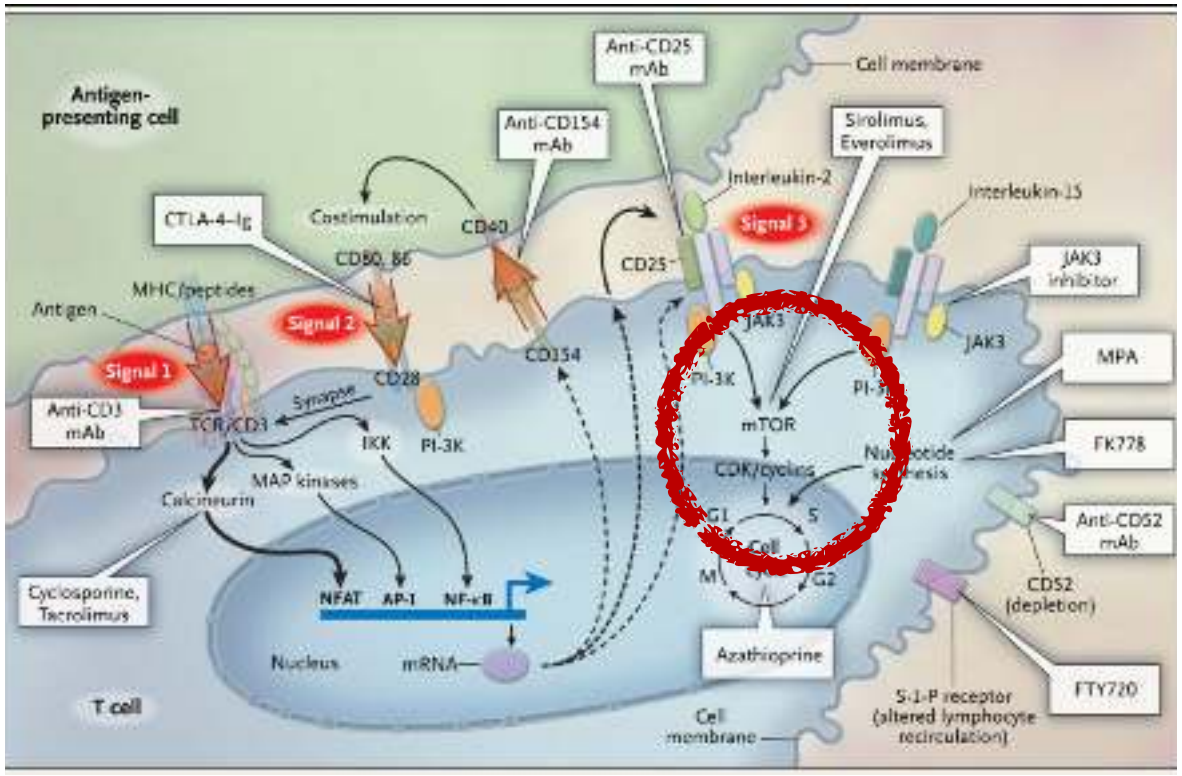

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Sınıflandırma

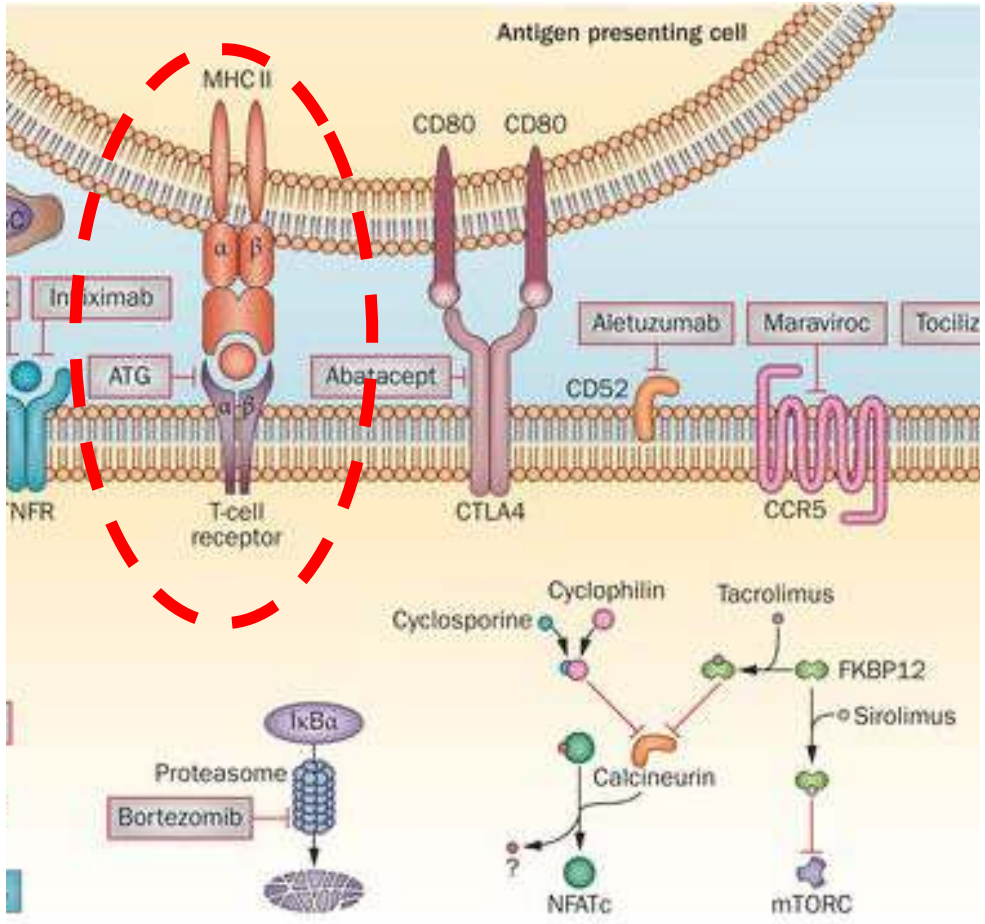
- **Küçük moleküllü ilaçlar**
- **Protein ilaçlar**

Protein ilaçlar

- **Antikor Tedavileri**
  - **Tavşan Antitimosit Globulin (rATG)**
  - **Rituksimab**
  - **Basiliksimab**
  - **Alemtuzumab**
  - **Belatacept**

Tavşan Antitimosit Globulin (rATG)

- **Lenfosit membran yapılarına karşı antikorlar**
  1. **Lizis (dolaşımdaki ve lenfoid dokudaki)**
  2. **Sinyal-1, 2 ve 3'ü inhibe eder**
  3. **İmmünsüpresif etkileri, ilaç vücuttan uzaklaştırıldıktan sonra da devam eder**



Ta G)

- **Lenfos antiko**
  1. **Li d**
  2. **Si**
  3. **İm vi da**

rATG Targets and Mechanism of Action

T-cell antigens	B-cell antigens
• CD 2	• CD 19
• CD 3	• CD 20
• CD 4	• CD 21
• CD 8	• CD 40
• CD 11a	
• CD 25	
• CD 44	
• CD 45	

rATG opsonizes the T cells causing cytolysis, apoptosis, and complement-mediated cell lysis

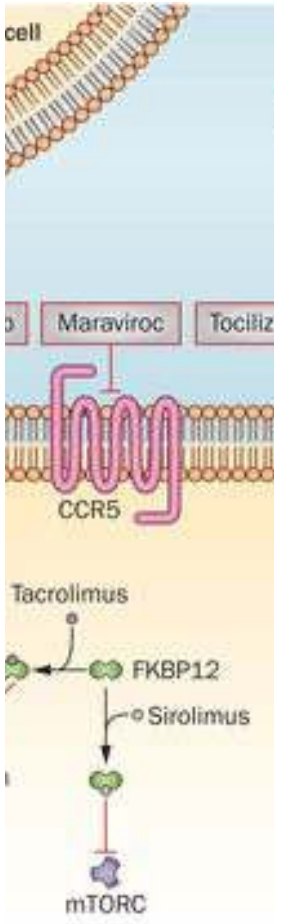
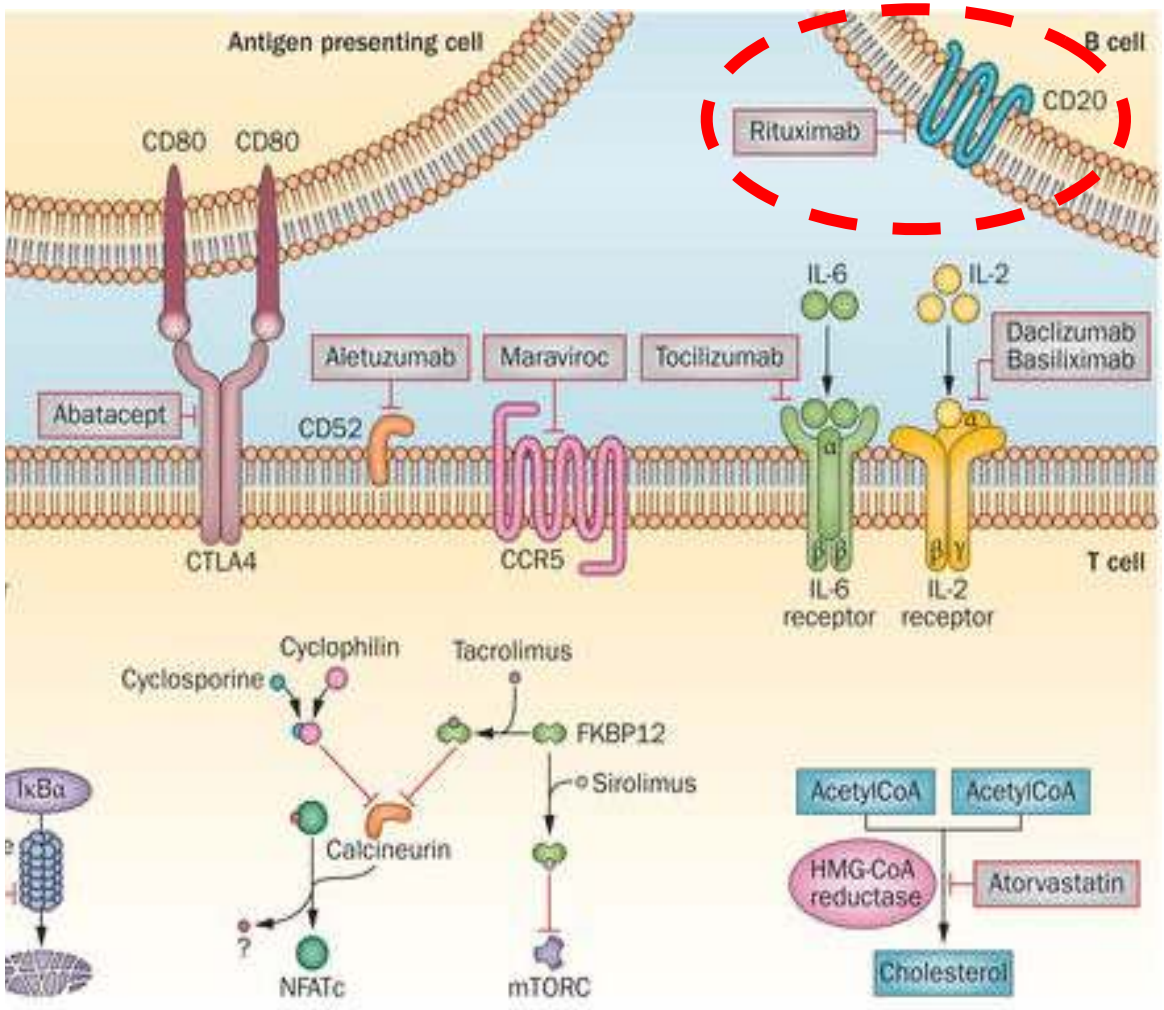


FIGURE 91-6 ■ The polyclonal rabbit antithymocyte globulin (rATG) Thymoglobulin is directed against numerous antigens found on both T cells and B cells, giving it a diverse mechanism of action that blocks signals 1, 2, and 3.

Rituximab

- **Kimerik monoklonal anti-CD20 antikoru**
  - **CD20'nin fonksiyonu net olarak bilinmiyor**
  - **B-hücresinin hücre siklusunun başlamasını ve farklılaşmasını regüle ettiği düşünülmekte**
  - **Rituksimab selektif olarak CD20'ye bağlanarak B-hücre yıkımına yol açar**



Basiliksimab

- IL-2 reseptörünün α zinciri (CD25) üzerinden etkisini gösteren fare-insan kimerik monoklonal antikordur
- IL-2'nin bağlanmasını inhibe eder
- T-hücre proliferasyon inhibisyonu
- Sinyal-3 yolağını bloke eder

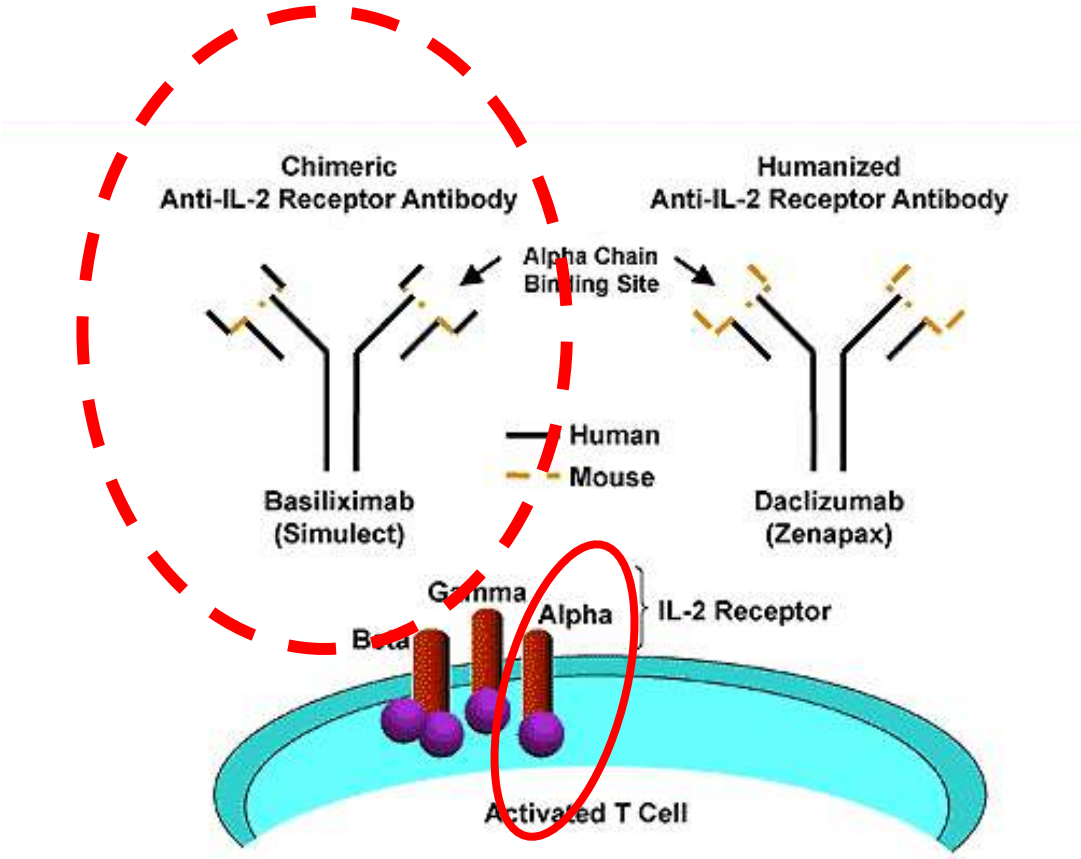


Figure 3. The IL-2 receptor antagonists.

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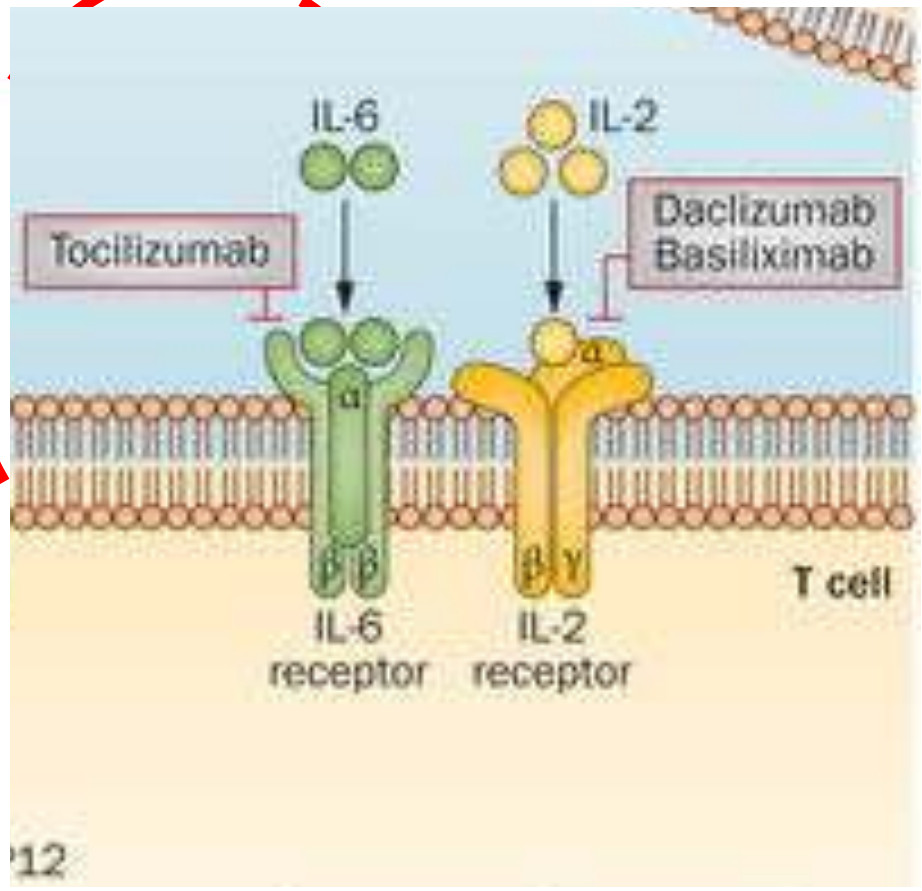
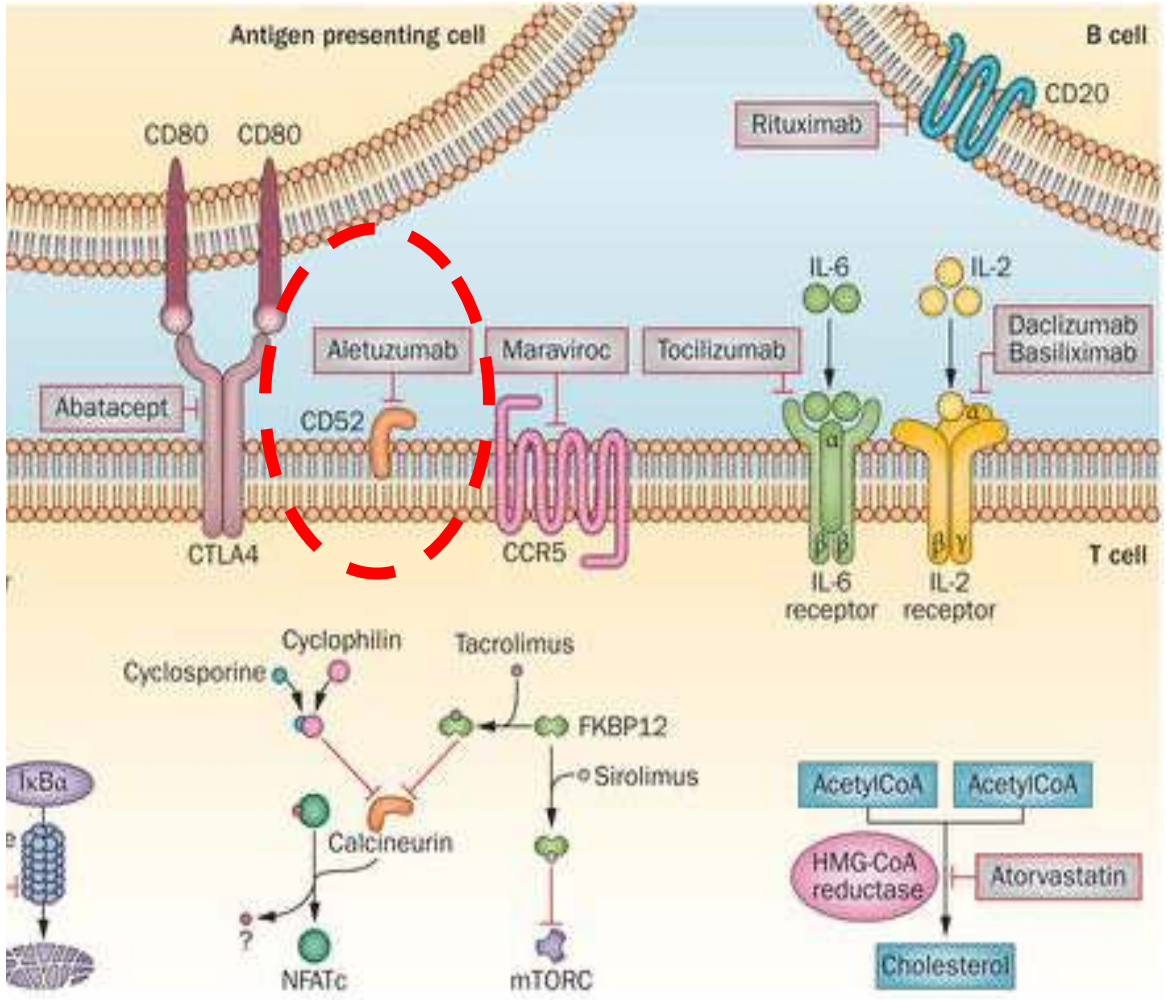


Figure 3. The IL-2 receptor antagonists.

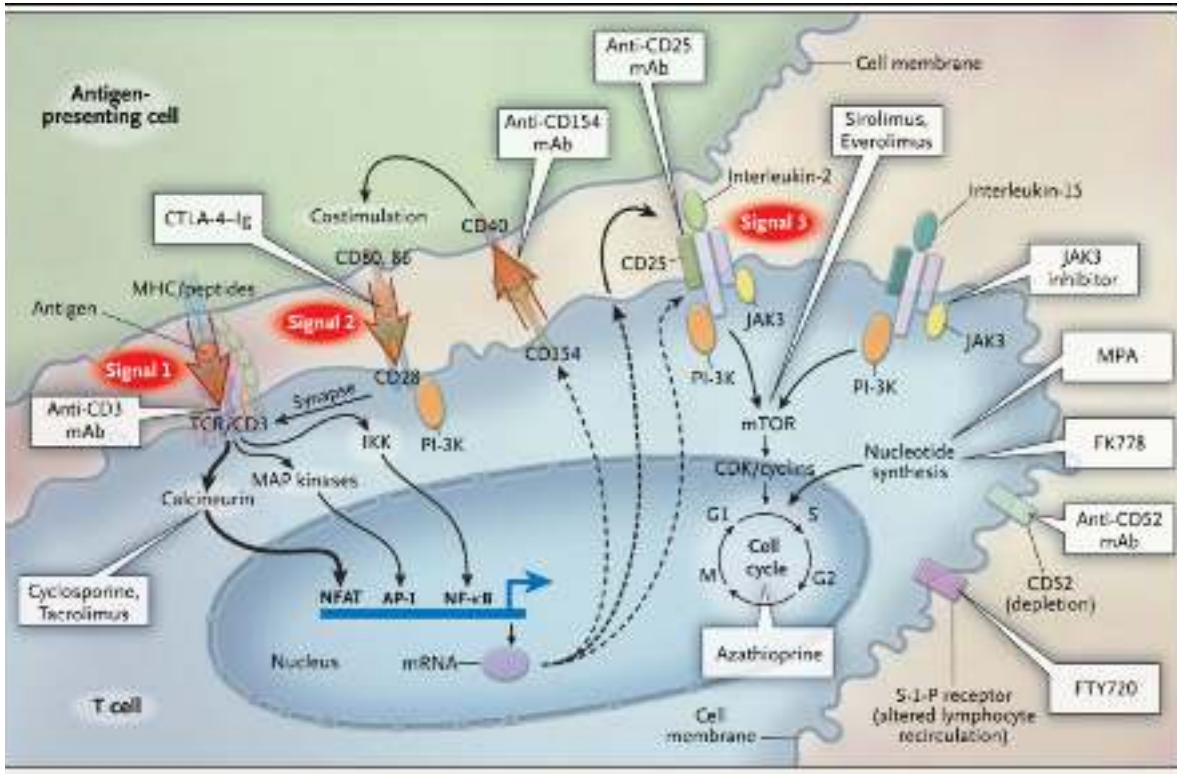
Alemtuzumab

- anti-CD52 antikoru
  - CD-52, periferik T ve B-hücrelerinin %95'inde bulunur
- Uzun süreli immünsüpresyona neden olur
  - B-hücrelerinde 6-12 ay
  - T-hücrelerinde 12-24 ay
- HBV enfeksiyonun aktive olmasına neden olabilir
- HCV pozitif hastalarda fatal yan etki (?)



Belatacept

- Sitotoksik T-lenfosit antijen-4 (CTLA4) - IgG
- CD80/CD86'ya bağlanarak selektif olarak T-hücre kostimülasyonunu (sinyal-2) bloke eder.
- Anerji ve T-hücre apoptozisi



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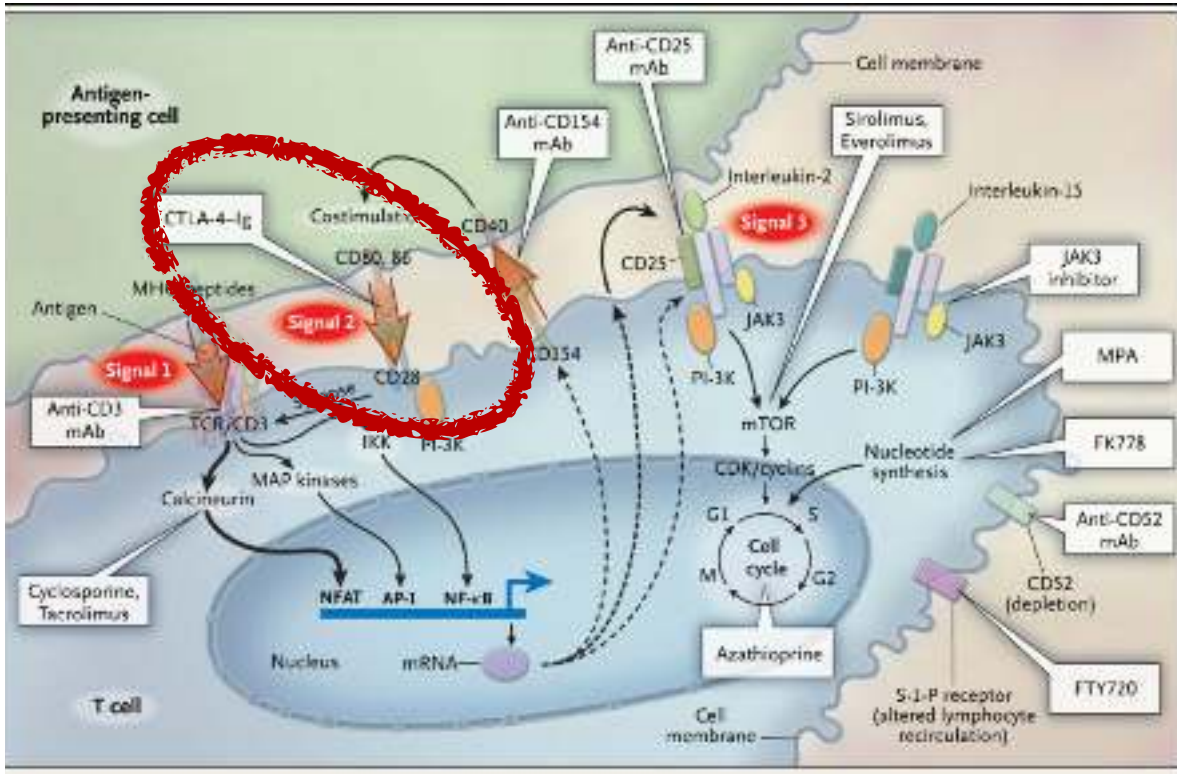

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